Synthesis, $(E)/(Z)$-isomerization, and DNA binding, antibacterial, and antifungal activities of novel oximes and O-substituted oxime ethers

Hatice BAŞPINAR KÜÇÜK[1], Ayşe Sergüzel YUSUFOĞLU[1,*],
Leyla AÇIK[2], Betül AYDIN[2], Leyla ARSLAN[2]
[1]Department of Chemistry, Faculty of Engineering, İstanbul University, İstanbul, Turkey
[2]Department of Biology, Faculty of Arts and Sciences, Gazi University, Ankara, Turkey

Abstract: A series of novel positional oximes (**2a**–**2d**), O-methyl oxime ethers (**3a**–**3d**), and O-benzyl oxime ethers (**4a**–**4d**) were synthesized in high yields starting from their corresponding methyl 3-, 4-, 6-, and 13-keto tetradecanoates. The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, mass, and elemental analyses for their structures and $(E)/(Z)$ isomerizations. Their DNA binding abilities were investigated in vitro by agarose gel electrophoresis. The antibacterial and antifungal activities were tested also in vitro against eleven bacterial strains and three fungal strains. The relationship between the structure and the mentioned biological activities was discussed. Compound **2a** showed good antibacterial activity against five types of bacteria. Compounds **2b**, **2c**, **2d**, and **4d** were effective against several microorganisms. Among these, **2a** showed the best DNA binding, antibacterial, and antifungal activities. Therefore, **2a** can be a pro-drug as an anticancer, antibacterial, and antifungal agent.

Key words: Oxime, oxime ether, keto ester, DNA binding, antibacterial activity, antifungal activity

1. Introduction

Oximes and O-substituted oxime ethers are important compounds in medicinal chemistry as potent pharmacophores[1−3] and building blocks of drug scaffolds.[4,5] They are gaining interest as antiprotozoan,[6] antibacterial,[7] antiretroviral,[8] antifungal,[9,10] antineoplastic,[11] and antimicrobial agents.[12] These are also serving as antidotes for organophosphorus poisoning.[13−15] According to the literature, a set of indirubin,[16] alkannin,[17] and shikonin oxime[17] derivatives that showed anticancer properties were synthesized. Shin et al. reported the inhibition effect of cyclopentenone oximes against tumor necrosis factor-α.[18] Several oxime ethers were found to be antiproliferative active.[19] Besides their biological activities, oximes and O-substituted oxime ethers are also important compounds in organic synthesis. Organic substances have been produced to be water-soluble over oxime groups. Limonin, being an antiinflammatory and analgesic agent, is more water-soluble over its oxime and oxime ether derivatives.[20] As starting compounds, oximes provided some new amino acids,[21] alkoxyimino esters,[22] alkoxyimino amides,[22] and pyrrole derivatives.[23]

Previously, our group reported the synthesis and enzyme inhibition activity of many keto and hydroxy fatty esters.[24−28] With the aim to make these keto esters more biologically active, we decided to synthesize their oximes (hydroxyimino-tetradecanoic acid methyl esters) (**2a**–**2d**), O-methyl oxime ethers (methoxyimino-

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tetradecanoic acid methyl esters) (**3a**–**3d**), and O-benzyl oxime ethers (benzyloxyimino-tetradecanoic acid methyl esters) (**4a**–**4d**). These twelve novel compounds were analyzed for their structures and isomerizations $((E)/(Z)$ ratio) by ^{1}H and ^{13}C NMR, FT-IR, mass, and elemental analyses.

DNA binding, antibacterial, and antifungal activities were tested as biological activities in this study. DNA binding efficiency is an important criterion for imaging new anticancer agents. DNA makes up chromosomes responsible for passing genetic information to the new cells and provides information for making proteins. Mutations in DNA can lead to cell death or to cancer. Cancer is one of the major health problems in the world. Therefore, much attention has been focused on developing drugs for various types of cancer. A large percentage of chemotherapeutic anticancer drugs are compounds that interact with DNA and prevent their proper function.[29] In order to characterize DNA-targeting drugs, the noncovalent compound–DNA interaction should be studied. One way to classify whether the compound physically interacts with DNA in vitro can be performed by agarose gel electrophoresis. The antibacterial activity of these compounds was also determined against eleven bacterial and three fungal test strains. The relationship between positional isomerization-$(E)/(Z)$ isomerization and these biological activities was discussed for these twelve original oximes, O-methyl oxime ethers, and O-benzyl oxime ethers.

2. Results and discussion

2.1. Chemistry

Oximes **2a**–**2d**, $O-$methyl oxime ethers **3a**–**3d**, and O-benzyl oxime ethers **4a**–**4d** were synthesized in high yields by utilizing positional isomers of 3-, 4-, 6-, and 13-keto tetradecanoic acid methyl esters in which the keto group is at the beginning, in the middle, and at the end of the fourteen-carbon chain with respect to the methyl ester (Scheme 1).
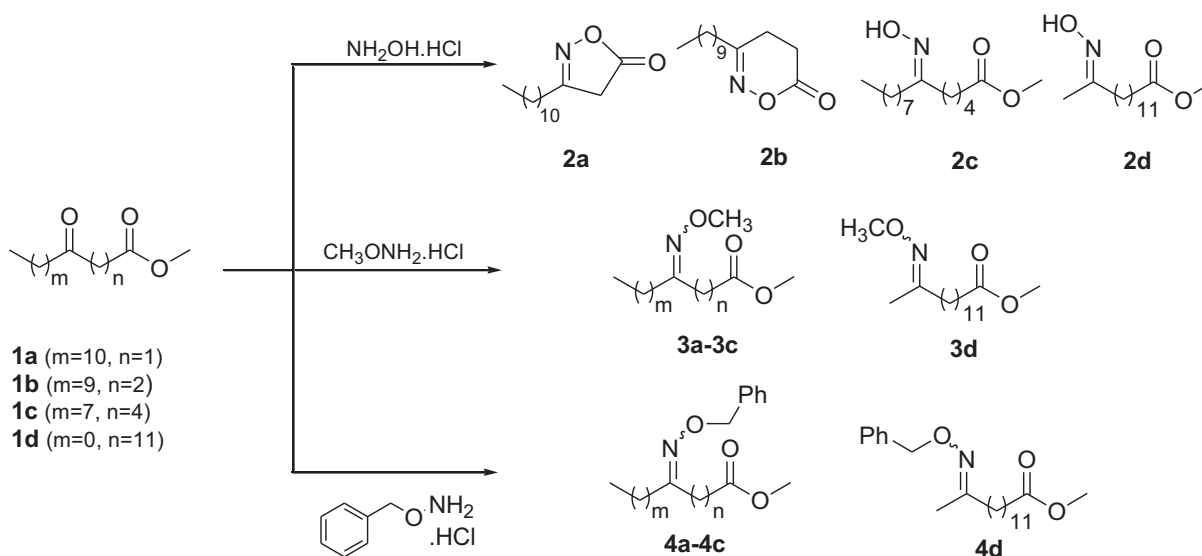

Scheme 1. Synthesis of oxime and O-substituted oxime ethers.

Our literature survey suggests a general isolation of $(E)/(Z)$ mixtures of oxime ethers. Similarly, our attempts to synthesize the O-methyl and $O-$benzyl oxime ethers of the mentioned keto esters yielded isomeric (E) and (Z) mixtures. Hydroxyimino derivatives, obtained with the effect of hydroxylamine hydrochloride

$(NH_2OH.HCl)$ on keto ester, were synthesized mainly as (E) isomer. In the literature, hydroxyimino compounds were also isolated exclusively as (E) isomer.[30−32] The isomerizations $((E)/(Z)$ ratio) of the synthesized compounds were analyzed with ^{1}H NMR. The ^{1}H NMR spectra showed double signals for methoxy and benzyloxy groups, which originate from the isomeric $(E)/(Z)$ mixtures of oxime ethers. The signals shifting to high field are due to the (Z) configuration, having a steric compression shift. On the other hand, the oxime ethers with (E) configuration resonated at lower fields than the (Z) isomer.[33−35]

In the formation of $(E)/(Z)$ isomers of the above-mentioned oximes and oxime ethers, the relative position of the keto group to the ester group is effective. There are three types of interactions: 1. The hydrogen bond between the oxime's hydrogen and the ester group, 2. The effect between oxime ether-methyl protons and the ester group, 3. The interactions between the partially positive charged carbon atom of the ester group and N and O atoms of the oxime. While these interactions lead to the molecule being held in the (Z) configuration, the number of methylene groups is also effective. As seen in Table 1, due to the experimental results of this study, an increase in the (E) isomer ratio was seen with increasing carbon number of the methylene bridge.

The reaction of 3-keto (**1a**) and 4-keto (**1b**) tetradecanoic acid methyl esters with $NH_2OH.HCl$ formed a cyclic structure as seen in Scheme 2 because of the presence of a (Z) configuration, and 3-undecyl-4H-isoxazol-5-one (**2a**) and 3-decyl-4,5-dihydro-[1,2]oxazin-6-one (**2b**) were obtained in this way. If the positions of hydroxyimino and methyl esters were close, methanol was eliminated because of this suitable (Z) structure and more stable five- or six-membered compounds were obtained.[36−38]
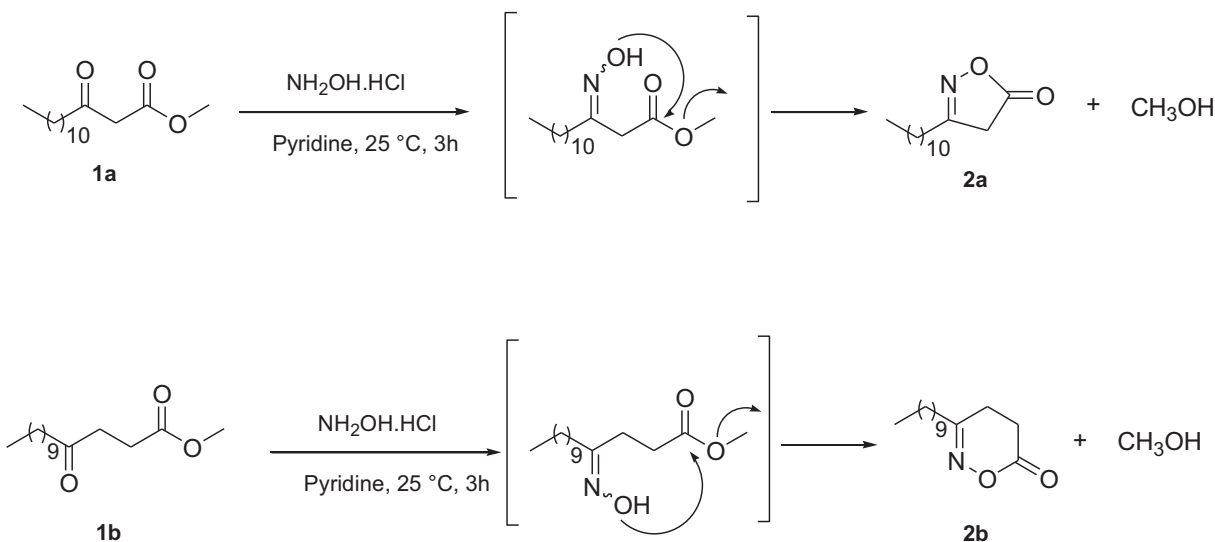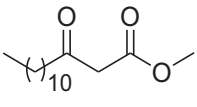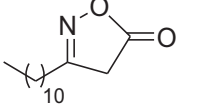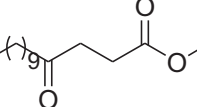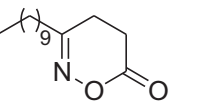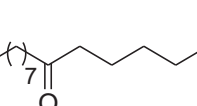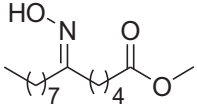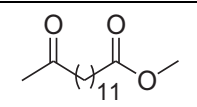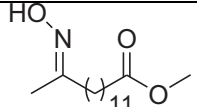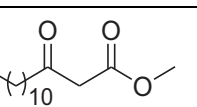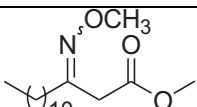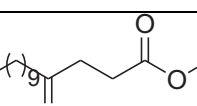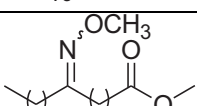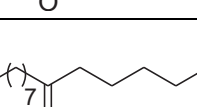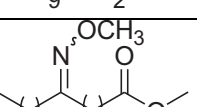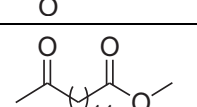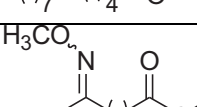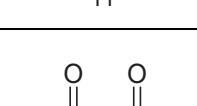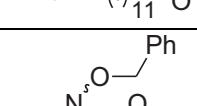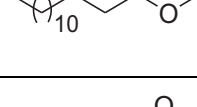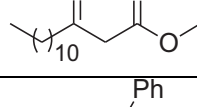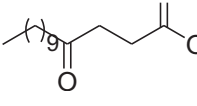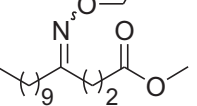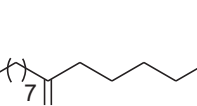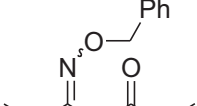

Scheme 2. Proposed mechanisms of synthesis of **2a** and **2b**.

When the keto group was in the middle (6-keto, **1c**) and at the end (13-keto, **1d**) of the chain, the interactions between hydroxyimino and methyl ester groups were interrupted because of the steric hindrances of the increasing methylene groups. Consequently, no methanol elimination occurred and hydroxyimino compounds were isolated in acyclic form and only as one isomer, namely as an (E) isomer.

Table 1 shows that O-methylhydroxylamine hydrochloride $(CH_3ONH_2.HCl)$ and O-benzylhydroxylamine hydrochloride $(C_6H_5CH_2ONH_2.HCl)$ give the results of the reactions with keto methyl ester isomers, yielding more (Z) isomer for 3- and 4-keto esters, a 50/50 ratio of $(E)/(Z)$ isomers for 6-keto ester, and a very little (Z)

Table 1. Isomer ratios ($(E)/(Z)$) and yields of synthesized oximes and O-substituted oxime ethers.

Entry	Keto ester	Product	Yield[a]	$(E)/(Z)$ Ratio[b]
1	**1a**	**2a**	75	-
2	**1b**	**2b**	77	-
3	**1c**	**2c**	82	E
4	**1d**	**2d**	80	E
5	**1a**	**3a**	93	35/65
6	**1b**	**3b**	98	48/52
7	**1c**	**3c**	98	50/50
8	**1d**	**3d**	89	75/25
9	**1a**	**4a**	83	32/68
10	**1b**	**4b**	96	39/61
11	**1c**	**4c**	97	50/50
12	**1d**	**4d**	93	70/30

[a] Isolated yield. [b] $(E)/(Z)$ ratio was determined by ^{1}H NMR.

isomer for 13-keto. 6-Keto is a critical position with its $(E)/(Z) = 50/50$ ratio, since it is nearly in the middle of the chain. Both its sides are nearly equal to each other. With increasing number of methylene groups and their steric hindrance, the interaction between oxime and ester group was decreased and the (E) isomer ratio was increased. The 13-keto position, the edge position, gave $(E)-$rich products for O-methyl and O-benzyl ether compounds.

2.2. Biological activities

2.2.1. Studies of interaction with pBR322 plasmid DNA

In DNA binding analyses, the compounds and DNA mixtures were incubated for 24 h. After incubation, the mixture was loaded on to the gel and electrophoresis was carried out at 60 V for 3 h. The illuminated gel was photographed (Figure). Electrophoresis of untreated plasmid DNA gave two bands corresponding to supercoiled form I with strong intensity and singly nicked form II DNA with weak intensity. When the plasmid was electrophoresed after its interaction with compound **2a**, significant decrease in the intensity of the bands was observed for 4 high concentrations of compound ranging from 100 to 6.25 mg/mL. In addition, electropheretic mobility of the form I band was found to be decreased sharply with the increase in the concentration of the compounds. The decrease in mobility is thought to be due to the binding of compound to DNA, thus reducing

Figure. Gel electrophoretic mobility of plasmid DNA, incubated with various concentrations of the compounds. Concentrations (in mg/mL) as follows: *lane P*, untreated plasmid DNA; lane 1, 100; lane 2, 50; lane 3, 25; lane 4, 12.5; lane 5, 6.25.

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the negative charge and increasing the molecular mass. The decrease in mobility could also be due to a change in the conformation of plasmid DNA.[39] In case of all other compounds, when plasmid interacted with all other compounds synthesized, no significant change in the intensity of bands was observed. However, the el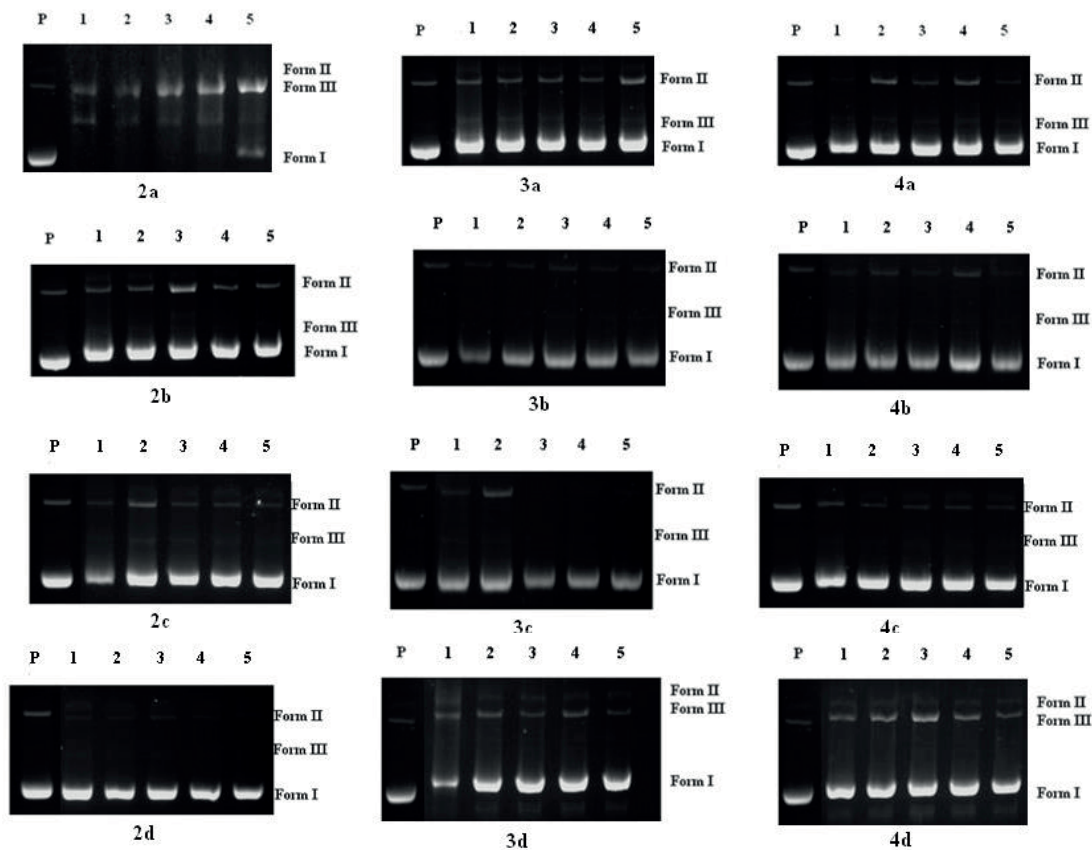ectropheretic mobility of the form I band was found to be decreased slightly with the decreasing concentrations of compounds. Based on DNA–compounds interaction studies, **2a** with its five-membered ring structure caused a greater change in plasmid DNA than the other compounds. **2b** with a six ring was not enough active. The other oximes and oxime ethers with open chain configuration had no activity. This result showed that a suitable ring system is necessary for tested DNA cleavage in this work as a key–lock model.

2.2.2. The antibacterial and antifungal activities of the compounds

The antibacterial activity of the compounds was determined against eleven bacterial and three fungal test strains. The concentrations of the compounds were 10 mg/mL. The antibacterial activity of the compounds is given in Table 2. According to these results, the oxime derivatives were more active than the oxime ethers. Three criteria were effective for this antibacterial activity. The β-position of the β-ketoxime methyl ester **2a** was important. The β-ketoxime methyl ester **2a** was obtained only in a five-membered cyclic form. The five ring system was more effective. The second criterion was the free hydroxy group of the oximes. Its $(E)/(Z)$ isomerization also induces this antibacterial effect as a third criterion. Acyclic ketoxime methyl esters with (E) configuration showed antibacterial activity, but the 6-ketoxime isomer **2c** with more steric hindrance was less active than the 13-ketoxime isomer **2d**. The O-substituted oxime ethers were not antibacterially active. Their $(E)/(Z)$ isomerizations were important here. The O-substituted oxime ether isomers with 3-, 4-, 6-positions were obtained nearly in a $(E)/(Z) = 50/50$ ratio; therefore they were inactive. However, the 13-benzyloxyimino-tetradecanoic acid methyl ester **4d** with $(E)/(Z) = 70/30$ ratio was active due to its greater (E) isomer content, less steric hindrance, and containing a phenyl ether group, as seen in Table 2. Compounds **2a** and **2d** showed the highest antibacterial activity of all the compounds against *Bacillus subtilis* ATCC 6633 and *Bacillus cereus* NRRL B-3711 with an inhibition zone diameter of 18 mm. Otherwise, compounds **3a**, **3b**, **3c**, **3d**, **4a**, **4b**, and **4c** used in this study exhibited no antibacterial activity against any strains.

In conclusion, this study involved the synthesis of twelve novel positional oximes and O-substituted oxime ether derivatives. Investigation of the DNA binding, antibacterial, and antifungal activities of these compounds showed that positional isomerism and stereoisomerism ($(E)/(Z)$ ratio) affected their biological activities. The best DNA cleavage was found for compound **2a**, which has a five-membered heterocyclic structure. Compound **2a** showed good antibacterial activity against five types of bacteria. Its ring structure was effective. The oxime **2d** of 100% (E) structure was more effective than **2b** and **2c**. Compounds **2b**, **2c**, **2d**, and **4d** can serve as potential antibacterial agents. **2a** had the best DNA binding, antibacterial, and antifungal activities. Therefore, **2a** can be a pro-drug as an anticancer, antibacterial, and antifungal agent.

3. Experimental

All reagents were obtained from commercial suppliers unless otherwise stated. Hydroxylamine hydrochloride, O-methylhydroxylamine hydrochloride, and O-benzylhydroxylamine hydrochloride were purchased from Sigma-Aldrich. From the keto tetradecanoic acid methyl ester isomers used as starting materials in the oxime and oxime ether synthesis 3- and 13-keto esters were synthesized by acetoacetester,[40,41] and 4-and 6-keto esters by Blaise reactions,[42] respectively. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (Merck; 230–400 mesh) with n-hexane–ethyl acetate.

Table 2. Antibacterial and antifungal activities of the compounds expressed as inhibition zones (mm).

Test microorganisms	Compounds												Positive control		
	2a	3a	4a	2b	3b	4b	2c	3c	4c	2d	3d	4d	Amp	C	Keto
E. coli ATCC 35218	-	-	-	-	-	-	-	-	-	-	-	-	-	8 ± 0	NS
E. coli ATCC 25922	-	-	-	-	-	-	-	-	-	-	-	-	18 ± 0	25 ± 0	NS
B. cereus NRRL B-3711	14 ± 1	-	-	10 ± 1	-	-	11 ± 1	-	-	18 ± 2	-	-	-	-	NS
B. subtilis ATCC 6633	18 ± 2	-	-	10 ± 1	-	-	12 ± 3	-	-	16 ± 1	-	-	23 ± 1	21 ± 0	NS
S. aureus ATCC 25923	14 ± 2	-	-	-	-	-	-	-	-	-	-	-	44 ± 1	24 ± 1	NS
E. faecalis ATCC 29212	12 ± 1	-	-	-	-	-	-	-	-	-	-	-	27 ± 0	20 ± 0	NS
P. aeruginosa ATCC 27853	-	-	-	-	-	-	-	-	-	-	-	-	60 ± 0	34 ± 0	NS
K. pneumoniae ATCC 13883	-	-	-	-	-	-	-	-	-	-	-	11 ± 1	-	31 ± 1	NS
S. typhimurium ATCC 14028	-	-	-	-	-	-	-	-	-	-	-	-	19 ± 1	38 ± 1	NS
E. hirae ATCC 9790	-	-	-	-	-	-	-	-	-	-	-	-	9 ± 1	22 ± 1	NS
P. vulgaris RSKK 96029	-	-	-	-	-	-	-	-	-	-	-	-	-	32 ± 1	NS
C. albicans ATCC 10231	-	-	-	-	-	-	-	-	-	-	-	-	NS	NS	11 ± 1
C. krusei ATCC 6258	-	-	-	-	-	-	-	-	-	-	-	-	NS	NS	18 ± 1
C. tropicalis Y-12968	9 ± 1	-	-	-	-	-	-	-	-	-	-	-	NS	NS	34 ± 2

Amp: Ampicillin, C: Chloramphenicol, Keto: Ketoconazole (NS: Not studied)

NMR spectra were recorded at 500 MHz for ^{1}H and at 125 MHz for ^{13}C using Me_4Si as the internal standard in $CDCl_3$. GC–MS were recorded on Shimadzu/QP2010 Plus. IR spectra were recorded on a Mattson 1000. Melting points were determined with a Buchi melting point B-540. Chemical yields refer to pure isolated substances.

3.1. General procedure A: preparation of oxime esters[43,44]

Keto ester (1.0 eq.) **1a–d** was dissolved in EtOH. Hydroxylamine hydrochloride (2.0 eq.) was added and the reaction mixture was stirred overnight. The reaction was diluted with saturated NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with water and brine, and dried over Na_2SO_4. The solvent was evaporated. The crude product was purified by column chromatography (silica gel, n-hexane-ethyl acetate = 7:3) to yield oxime **2a–d.**

3.1.1. 3-Undecyl-4H-isoxazol-5-one (2a)

The title compound **2a** was synthesized according to the general procedure A. Hydroxylamine hydrochloride (0.277 g, 4.0 mmol) was treated with 3-keto tetradecanoic acid methyl ester (0.512 g, 2.0 mmol). **2a** was isolated as an orange crystal. 75% yield. mp 44–45 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.31 (s, 2H, –CH_2 of isoxazole), 2.39 (t, J = 7.5 Hz, 2H, –CH_2 H-1'), 1.56–1.50 (m, 2H, –CH_2 H-2'), 1.31–1.19 (m, 16H, –CH_2), 0.81 (t, J = 5.0 Hz, 3H, –CH_3). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.3 (C=O), 166.1 (C=N), 34.8 (CH_2 of isoxazole), 30.9 (CH_2, C9'), 28.5 (CH_2, C1'), 28.4–28.0 (CH_2, C8'-C5'), 24.3 (CH_2, C2'), 21.7 (CH_2, C10'), 13.1 (CH_3, C11'). **IR** (KBr, cm^{-1}) ν 2923, 2853, 1738, 1623, 1476, 1176, 892. Anal. Calcd. for $C_{14}H_{25}NO_2$ C = 70.25, H = 10.53, N = 5.85. Found: C = 70.21, H = 10.51, N = 5.83. **MS** (m/z) = 41, 55, 82, 96, 99, 112, 240 (M$^+$ +1).

3.1.2. 3-Decyl-4,5-dihydro-[1,2]oxazin-6-one (2b)

The title compound **2b** was synthesized according to the general procedure A. Hydroxylamine hydrochloride (0.277 g, 4.0 mmol) was treated with 4-keto tetradecanoic acid methyl ester (0.512 g, 2.0 mmol). **2b** was isolated as a colorless oil. 77% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.07 (t, J = 5.0 Hz, 2H, –CH_2, H-1), 2.55–2.50 (m, 2H, –CH_2, H-2), 2.27 (t, J = 10.0 Hz, 2H, –CH_2, H-1'), 1.47–1.41 (m, 2H, –CH_2, H-2'), 1.23–1.17 (m, 14H, –CH_2), 0.81 (t, J =7.5 Hz, 3H, –CH_3). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.9 (C=O), 159.9 (C=N), 33.5 (CH_2, C8'), 30.9 (CH_2, C7'), 29.5 (CH_2 of oxazine, C1), 28.8 (CH_2, C1'), 28.5-28.2 (CH_2, C6'-C3'), 27.2 (CH_2, C2'), 24.6 (CH_2, C9'), 21.7 (CH_2 of oxazine, C2), 13.1 (CH_3, C10'). **IR** (neat, cm^{-1}) ν 2869, 2807, 1700, 1646, 1423, 1138, 1007, 923. Anal. Calcd. for $C_{14}H_{25}NO_2$ C = 70.25, H = 10.53, N = 5.85. Found: C = 70.22, H = 10.50, N = 5.81. **MS** (m/z) = 82, 97, 110, 113, 142, 222, 240 (M$^+$ +1).

3.1.3. 6-Hydroxyimino-tetradecanoic acid methyl ester (2c)

The title compound **2c** was synthesized according to the general procedure A. Hydroxylamine hydrochloride (0.277 g, 4.0 mmol) was treated with 6-keto tetradecanoic acid methyl ester (0.512 g, 2.0 mmol). **2c** was isolated as a colorless oil. 82% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.58 (br s, 1H, NOH), 3.60 (s, 3H, O–CH_3), 2.30–2.24 (m, 4H, –CH_2 H-5, –CH_2 H-2), 2.14–2.08 (m, 2H, –CH_2, H-7), 1.64–1.56 (m, 2H, –CH_2, H-3), 1.51–1.39 (m, 4H, –CH_2 H-8, –CH_2, H-4), 1.23–1.20 (m, 10H, –CH_2), 0.81 (t, J = 5.0 Hz, 3H, –CH_3).

^{13}C NMR (125 MHz, CDCl$_3$) δ 174.0 (C=O), 161.1 (C=N), 51.6 (OCH$_3$), 33.7 (CH$_2$, C2), 31.9 (CH$_2$, C7), 29.9–24.5 (CH$_2$, C5-C3 C12-C8), 22.6 (CH$_2$, C13), 14.1 (CH$_3$, C14). **IR** (neat, cm^{-1}) ν 3315, 2938, 2861, 1746, 1684, 1469, 1253, 1076, 976. Anal. Calcd. for C$_{15}$H$_{29}$NO$_3$ C = 66.38, H = 10.77, N = 5.16. Found: C = 66.37, H = 10.73, N = 5.15. **MS** (m/z) = 41, 57, 73, 96, 110, 240, 254, 271 (M$^+$).

3.1.4. 13-Hydroxyimino-tetradecanoic acid methyl ester (2d)

The title compound **2d** was synthesized according to the general procedure A. Hydroxylamine hydrochloride (0.277 g, 4.0 mmol) was treated with 13-keto tetradecanoic acid methyl ester (0.512 g, 2.0 mmol). **2d** was isolated as a white crystal. 80% yield. mp 59–60 °C. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 8.67(br s, 1H, NOH), 3.67 (s, 3H, O–CH$_3$), 2.31 (t, J = 7.5 Hz, 2H, –CH$_2$, H-2), 2.18 (t, J = 7.5 Hz, 2H, –CH$_2$, H-12), 1.88 (s, 3H, –CH$_3$), 1.63–1.60 (m, 2H, –CH$_2$, H-3), 1.51–1.48 (m, 2H, –CH$_2$, H-11), 1.26 (m, 14 H, –CH$_2$). **^{13}C NMR** (125 MHz, CDCl$_3$) δ 174.4 (C=O), 158.7 (C=N), 51.5 (OCH$_3$), 35.8 (CH$_2$, C2), 34.1 (CH$_2$, C12), 29.5–29.1 (CH$_2$, C10-C3), 24.9 (CH$_2$, C11), 13.3 (CH$_3$, C14). **IR** (KBr, cm^{-1}) ν 3292, 2930, 2861, 1746, 1684, 1476, 1223, 1184, 953. Anal. Calcd. for C$_{15}$H$_{29}$NO$_3$ C = 66.38, H = 10.77, N = 5.16. Found: C = 66.37, H = 10.75, N = 5.14. **MS** (m/z) = 41, 55, 57, 73, 86, 224, 254, 272 (M$^+$ +1).

3.2. General procedure B: preparation of *O*-methyl and *O*-benzyl oximino esters[45]

To a solution of keto ester (1.0 eq.) **1a–d** in pyridine was added a solution of alkoxyamine hydrochloride (1.1 eq.) in pyridine at room temperature. The resulting solution was stirred for 6–12 h. After the consumption of the starting material, the reaction mixture was diluted with water, and then extracted with ethyl acetate. The organic phase was combined, dried over anhydydrous Na$_2$SO$_4$, filtered, and the filtrate concentrated under reduced pressure to give the crude product. The residue was purified by column chromatography on silica gel (n-hexane-ethyl acetate = 7:3) to give the desired products **3a–d** and **4a–d**.

3.2.1. 3-Methoxyimino-tetradecanoic acid methyl ester (3a)

The title compound **3a** was synthesized according to the general procedure B. *O*-methylhydroxylamine hydrochloride (0.183 g, 2.2 mmol) was treated with 3-keto tetradecanoic acid methyl ester (0.512 g, 2.0 mmol). **3a** was isolated as a colorless oil ((E)/(Z) = 35/65). 93% yield. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 3.76 & 3.75 (s, 3H, NOCH$_3$), 3.63 & 3.61 (s, 3H, COOCH$_3$), 3.22 & 3.13 (s, 2H, –CH$_2$, H-2), 2.30 (t, J = 7.5 Hz, 0.7H, –CH$_2$, H-4), 2.18 (t, J = 10.0 Hz, 1.3H, –CH$_2$, H-4), 1.47–1.34 (m, 2H, –CH$_2$, H-5), 1.24–1.19 (m, 16H, –CH$_2$), 0.81 (t, J = 7.5 Hz, 3H, –CH$_3$). **^{13}C NMR** (125 MHz, CDCl$_3$) δ 169.1 & 168.3 (C=O), 154.0 & 152.5 (C=N), 60.3 (=N–OCH$_3$), 51.0 (OCH$_3$), 38.4 (CH$_2$, C2), 33.7 (CH$_2$, C12), 32.7–24.4 (CH$_2$, C4-C11), 21.7 (CH$_2$, C13), 13.1 (CH$_3$, C14). **IR** (neat, cm^{-1}) ν 2930, 2861, 1753, 1646, 1469, 1169, 1053, 907. Anal. Calcd. for C$_{16}$H$_{31}$NO$_3$ C = 67.33, H = 10.95, N = 4.91. Found: C = 67.30, H = 10.94, N = 4.90. **MS** (m/z) = 41, 55, 74, 113, 145, 158, 212, 254, 286 (M$^+$ +1).

3.2.2. 4-Methoxyimino-tetradecanoic acid methyl ester (3b)

The title compound **3b** was synthesized according to the general procedure B. *O*-methylhydroxylamine hydrochloride (0.183 g, 2.2 mmol) was treated with 4-keto tetradecanoic acid methyl ester (0.512 g, 2.0 mmol). **3b** was isolated as a colorless oil ((E)/(Z) = 48/52). 98% yield. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 3.73 &

3.70 (s, 3H, NOCH$_3$), 3.61 & 3.60 (s, 3H, COOCH$_3$), 2.50–2.40 (m, 4H, –CH$_2$ H-2, –CH$_2$ H-3), 2.19 (t, J = 7.5 Hz, 1H, –CH$_2$, H-5), 2.09 (t, J = 7.5 Hz, 1H, –CH$_2$, H-5), 1.43–1.35 (m, 2H, –CH$_2$, H-6), 1.21–1.19 (m, 14H, –CH$_2$), 0.81 (t, J = 7.5 Hz, 3H, –CH$_3$). **^{13}C NMR** (125 MHz, CDCl$_3$) δ 172.4 & 172.1 (C=O), 158.4 & 157.8 (C=N), 60.1 (=N–OCH$_3$), 50.6 & 50.5 (OCH$_3$), 33.5 (CH$_2$, C5), 31.0 (CH$_2$, C12), 29.3–22.7 (CH$_2$, C11-C6, C3-C2), 21.7 (CH$_2$, C13), 13.1 (CH$_3$, C14). **IR** (neat, cm^{-1}) ν 2930, 2853, 1746, 1646, 1446, 1176, 1061, 892. Anal. Calcd. for C$_{16}$H$_{31}$NO$_3$ C = 67.33, H = 10.95, N = 4.91. Found: C = 67.31, H = 10.91, N = 4.89. **MS** (m/z) = 41, 55, 100, 127, 159, 198, 254, 283 (M$^+$ –2).

3.2.3. 6-Methoxyimino-tetradecanoic acid methyl ester (3c)

The title compound **3c** was synthesized according to the general procedure B. *O*-methylhydroxylamine hydrochloride (0.183 g, 2.2 mmol) was treated with 6-keto tetradecanoic acid methyl ester (0.512 g, 2.0 mmol). **3c** was isolated as a colorless oil ((E)/(Z) = 50/50). 98% yield. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 3.73 (s, 3H, NOCH$_3$), 3.60 (s, 3H, COOCH$_3$), 2.29–2.17 (m, 4H, –CH$_2$ H-2, –CH$_2$ H-7), 2.12–2.05 (m, 2H, –CH$_2$ H-5), 1.63–1.55 (m, 2H, –CH$_2$ H-3), 1.51–1.40 (m, 4H –CH$_2$ H-4, –CH$_2$ H-8), 1.21 (m, 10H, –CH$_2$), 0.82 (t, J = 7.5 Hz, 3H, –CH$_3$). **^{13}C NMR** (125 MHz, CDCl$_3$) δ 173.8 (C=O), 160.8 (C=N), 60.9 (=N–OCH$_3$), 51.4 (OCH$_3$), 34.0 (CH$_2$, C2), 33.6 (CH$_2$, C7), 31.8 (CH$_2$, C12), 29.8–24.9 (CH$_2$, C5-C3, C11-C8), 22.6 (CH$_2$, C13), 14.0 (CH$_3$, C14). **IR** (neat, cm^{-1}) ν 2938, 2861, 1753, 1646, 1469, 1215, 1053, 892. Anal. Calcd. for C$_{16}$H$_{31}$NO$_3$ C = 67.33, H = 10.95, N = 4.91. Found: C = 67.30, H = 10.92, N = 4.87. **MS** (m/z) = 41, 55, 87, 100, 198, 238, 254, 285 (M$^+$).

3.2.4. 13-Methoxyimino-tetradecanoic acid methyl ester (3d)

The title compound **3d** was synthesized according to the general procedure B. *O*-methylhydroxylamine hydrochloride (0.183 g, 2.2 mmol) was treated with 13-keto tetradecanoic acid methyl ester (0.512 g, 2.0 mmol). **3d** was isolated as a colorless oil ((E)/(Z) = 75/25). 89% yield. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 3.75 & 3.73 (s, 3H, NOCH$_3$), 3.59 (s, 3H, COOCH$_3$), 2.23 (t, J = 5.0 Hz, 2H, –CH$_2$ H-2), 2.08 (t, J = 7.5 Hz, 2H, –CH$_2$ H-12), 1.77 & 1.74 (s, 3H, –CH$_3$), 1.58–1.52 (m, 2H, –CH$_2$ H-3), 1.44–1.37 (m, 2H, –CH$_2$ H-11), 1.22–1.20 (m, 14H, –CH$_2$). **^{13}C NMR** (125 MHz, CDCl$_3$) δ 173.2 (C=O), 157.4 & 156.8 (C=N), 60.0 & 59.9 (=N–OCH$_3$), 50.3 (OCH$_3$), 34.8 (CH$_2$, C2), 33.1 (CH$_2$, C12), 28.6–23.9 (CH$_2$, C10-C3), 18.8 (CH$_2$, C11), 12.7 (CH$_3$, C14). **IR** (neat, cm^{-1}) ν 2930, 2853, 1753, 1646, 1469, 1176, 1053, 900. Anal. Calcd. for C$_{16}$H$_{31}$NO$_3$ C = 67.33, H = 10.95, N = 4.91. Found: C = 67.32, H = 10.92, N = 4.89. **MS** (m/z) = 42, 57, 87, 100, 254, 270, 285 (M$^+$).

3.2.5. 3-Benzyloxyimino-tetradecanoic acid methyl ester (4a)

The title compound **4a** was synthesized according to the general procedure B. *O*-Benzylhydroxylamine hydrochloride (0.351 g, 2.2 mmol) was treated with 3-keto tetradecanoic acid methyl ester (0.512 g, 2.0 mmol). **4a** was isolated as a colorless oil ((E)/(Z) = 32/68). 83% yield. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.26–7.15 (m, 5H, Ar–H), 5.00 (s, 2H, NO–CH$_2$–Ar), 3.60 & 3.52 (s, 3H, COOCH$_3$), 3.22 & 3.12 (s, 2H, =C–CH$_2$=C, H-2), 2.34 (t, J = 10.0 Hz, 0.6H, –CH$_2$ H-4), 2.18 (t, J = 10.0 Hz, 1.3H, –CH$_2$ H-4), 1.44–1.35 (m, 2H, –CH$_2$ H-5), 1.22–1.17 (m, 16H, –CH$_2$), 0.80 (t, J = 5.0 Hz, 3H, –CH$_3$). **^{13}C NMR** (125 MHz, CDCl$_3$) δ 169.1 & 168.3 (C=O), 154.6 & 153.0 (C=N), 137.0 (Aromatic-C, C1'), 136.9–126.6 (Aromatic-C, C2'-C6'), 74.6 & 74.5 (NO–CH$_2$–Ar), 51.0 & 50.9 (OCH$_3$), 38.4 (CH$_2$, C2), 33.7 (CH$_2$, C12), 33.2 (CH$_2$, C4), 30.9–25.0 (CH$_2$,

C11-C5), 21.7 (CH$_2$, C13), 13.1 (CH$_3$, C14). **IR** (neat cm^{-1}) ν 3030, 2930, 2853, 1753, 1646, 1469, 1169, 1030, 938, 746. Anal. Calcd. for C$_{22}$H$_{35}$NO$_3$ C = 73.09, H = 9.76, N = 3.87. Found: C = 73.06, H = 9.73, N = 3.84. **MS** (m/z) = 41, 57, 77, 91, 104, 221, 330, 344, 361 (M$^+$).

3.2.6. 4-Benzyloxyimino-tetradecanoic acid methyl ester (4b)

The title compound **4b** was synthesized according to the general procedure B. *O*-Benzylhydroxylamine hydrochloride (0.351 g, 2.2 mmol) was treated with 4-keto tetradecanoic acid methyl ester (0.512 g, 2.0 mmol). **4b** was isolated as a colorless oil ((E)/(Z) = 39/61). 96% yield. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.24–7.15 (m, 5H, Ar–H), 4.97 & 4.93 (s, 2H, NO–CH$_2$–Ar), 3.55 & 3.51 (s, 3H, COOCH$_3$), 2.52–2.38 (m, 4H, =C–CH$_2$–CH$_2$=C, H-2 H-3), 2.22 (t, J = 7.5 Hz, 1.2H, –CH$_2$ H-5), 2.09 (t, J = 7.5 Hz, 0.8H, –CH$_2$ H-5), 1.41–1.35 (m, 2H, –CH$_2$ H-6), 1.23–1.17 (m, 14H, –CH$_2$), 0.80 (t, J = 7.5 Hz, 3H, –CH$_3$). **^{13}C NMR** (125 MHz, CDCl$_3$) δ 172.3 & 172.1 (C=O), 158.8 & 158.1 (C=N), 137.5 (Aromatic-C, C1'), 137.2–126.4 (Aromatic-C, C2'-C6'), 74.4 (NO–CH$_2$–Ar), 50.6 & 50.5 (OCH$_3$), 33.5 (CH$_2$, C5), 30.9 (CH$_2$, C12), 29.1–22.9 (CH$_2$, C11-C6 C3-C2), 21.7 (CH$_2$, C13), 13.1 (CH$_3$, C14). **IR** (neat, cm^{-1}) ν 3038, 2930, 2853, 1746, 1661, 1461, 1176, 1053, 930, 746. Anal. Calcd. for C$_{22}$H$_{35}$NO$_3$ C = 73.09, H = 9.76, N = 3.87. Found: C = 73.05, H = 9.74, N = 3.87. **MS** (m/z) = 41, 51, 77, 91, 105, 218, 235, 254, 274, 281, 302 (M$^+$ - COOCH$_3$).

3.2.7. 6-Benzyloxyimino-tetradecanoic acid methyl ester (4c)

The title compound **4c** was synthesized according to the general procedure B. *O*-Benzylhydroxylamine hydrochloride (0.351 g, 2.2 mmol) was treated with 6-keto tetradecanoic acid methyl ester (0.512 g, 2.0 mmol). **4c** was isolated as a colorless oil ((E)/(Z) = 50/50). 97% yield. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.34–7.27 (m, 5H, Ar–H), 5.07 & 5.06 (s, 2H, NO–CH$_2$–Ar), 3.65 & 3.63 (s, 3H, COOCH$_3$), 2.35–2.28 (m, 4H, –CH$_2$ H-2, –CH$_2$ H-7), 2.19–2.13 (m, 2H, –CH$_2$ H-5), 1.67–1.47 (m, 6H, –CH$_2$ H-3 H-4 H8), 1.27 (m, 10H, –CH$_2$), 0.89 (t, J = 10.0 Hz, 3H, –CH$_3$). **^{13}C NMR** (125 MHz, CDCl$_3$) δ 173.8 (C=O), 161.2 (C=N), 138.5 (Aromatic-C, C1'), 138.4–127.4 (Aromatic-C, C2'-C6'), 75.2 (NO–CH$_2$–Ar), 51.4 (OCH$_3$), 34.1 (CH$_2$, C2), 33.7 (CH$_2$, C7), 31.9 (CH$_2$, C12), 29.8–24.5 (CH$_2$, C11-C8 C5-C3), 22.7 (CH$_2$, C13), 14.1 (CH$_3$, C14). **IR** (neat, cm^{-1}) ν 3030, 2938, 2861, 1738, 1646, 1461, 1369, 1215, 1053, 930, 753. Anal. Calcd. for C$_{22}$H$_{35}$NO$_3$ C = 73.09, H = 9.76, N = 3.87. Found: C = 73.06, H = 9.72, N = 3.85. **MS** (m/z) = 41, 57, 77, 91, 163, 246, 263, 344, 361 (M$^+$).

3.2.8. 13-Benzyloxyimino-tetradecanoic acid methyl ester (4d)

The title compound **4d** was synthesized according to the general procedure B. *O*-Benzylhydroxylamine hydrochloride (0.351 g, 2.2 mmol) was treated with 13-keto tetradecanoic acid methyl ester (0.512 g, 2.0 mmol). **4d** was isolated as a colorless oil ((E)/(Z) = 70/30). 93% yield. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.27–7.17 (m, 5H, Ar–H), 4.99 & 4.96 (s, 2H, NO–CH$_2$–Ar), 3.56 (s, 3H, COOCH$_3$), 2.21 (t, J = 7.5 Hz, 2H, –CH$_2$ H-2), 2.06 (t, J = 7.5 Hz, 2H, –CH$_2$ H-12), 1.77 & 1.75 (s, 3H, –CH$_3$), 1.54–1.52 (m, 2H, –CH$_2$ H-3), 1.41–1.38 (m, 2H, –CH$_2$ H-11), 1.20–1.17 (m, 14H, –CH$_2$). **^{13}C NMR** (125 MHz, CDCl$_3$) δ 173.2 (C=O), 157.9 & 157.3 (C=N), 137.4 (Aromatic-C, C1'), 127.2-126.4 (Aromatic-C, C2'-C6'), 74.2 & 74.1 (NO–CH$_2$–Ar), 50.3 (OCH$_3$), 34.8 (CH$_2$, C2), 33.0 (CH$_2$, C12), 28.6–23.9 (CH$_2$, C10-C3), 18.9 (CH$_2$, C11), 13.1 (CH$_3$, C14). **IR** (neat, cm^{-1}) ν 3038, 2938, 2861, 1738, 1653, 1469, 1376, 1269, 1061, 946, 761. Anal. Calcd. for C$_{22}$H$_{35}$NO$_3$

C = 73.09, H = 9.76, N = 3.87. Found: C = 73.07, H = 9.73, N = 3.83. **MS** (m/z) = 41, 55, 77, 91, 163, 270, 333, 344, 361 (M$^+$).

3.3. Studies of interaction with pBR322 plasmid DNA

The interaction of compounds with plasmid DNA was studied by agarose gel electrophoresis. Stock solutions of the compounds were prepared and used within 1 h. Then decreasing concentrations of the compounds ranging from 100 to 6.25 mg/mL were incubated with plasmid DNA in the dark at 37 °C for 24 h. The aliquots of the DNA/compound mixtures were mixed with the loading buffer (0.1% bromophenol blue, 0.1% sucrose) and loaded onto 1% agarose gel. Electrophoresis was carried out under TAE buffer (0.05 M Tris base, 0.05 M glacial acetic acid, and 1 mM EDTA, pH 8.0) for 3 h at 70 V. The gel was stained with ethidium bromide (0.5 μg/mL), visualized under UV light using a transilluminator (BioDoc Analyzer, Biometra), and the image was captured with a video camera as a TIFF file. The experiments were repeated three times.

3.4. Antibacterial and antifungal activities

The antibacterial activities of all the compounds were assessed against the bacterial strains *Bacillus cereus* NRRL B-3711, *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Enterococcus hirae* ATCC 9790, *Escherichia coli* ATCC 35218, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* ATCC 13883, *Salmonella typhimurium* ATCC 14028, and *Proteus vulgaris* RSKK 96029 and the fungal strains *Candida albicans* ATCC 10231, *Candida krusei* ATCC 6258, and *Candida tropicalis* Y-12968 by agar well diffusion. For comparison, ampicillin, chloramphenicol (antibacterial), and ketoconazole (antifungal) were used as the standard antibiotics. Test strains were incubated on nutrient agar plates at 37 °C for 24 h for bacteria and on Sabouraud dextrose agar plates at 30 °C for 48 h for fungi. After incubation, bacterial suspensions were adjusted to a turbidity of 0.5 McFarland. Mueller Hinton agar (for bacterial strains) and Sabouraud dextrose agar (for fungal strains) were mixed with 1% culture suspension and poured into plates. Wells with a 6.0 mm diameter were prepared and the solution of the 10 mg/mL compound (50 μL) was added to the well. After incubation, the diameter of the inhibition zone was measured in millimeters. All the experiments were repeated three times, and the mean values are presented.

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