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Short communication

# Synthesis and antimicrobial activity of new (E)-4-[piperidino (4'-methylpiperidino-, morpholino-) N-alkoxy]stilbenes

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**Abstract**

The synthesis of twenty-one new (E)-4-[piperidino-(4`-methylpiperidino-, morpholino-)N-alkoxy] stilbenes is reported. The compounds were tested for antimicrobial activities against Gram-negative, Gram-positive bacteria, and fungi. In particular, compounds **3b**, **3c**, **3f**, **3g**, **3h**, **3k**, **3l** showed good antibacterial activity against *Staphylococcus aureus* and **3h**, **3k**, **3m**, **3n** also against *Bacillus subtilis*, as well as **3h**, **3n** also against *Streptococcus faecalis*.


*Keywords:* (E)-stilbenes; Piperidines; Morpholines; Antimicrobial activity

## 1. Introduction

(E)-stilbenes, hydroxylated at two to five positions, and their oligomers, are natural compounds, found in various families of plants. Hydroxylated stilbenes have been widely investigated because of their biological role in plant defense against pathogens and for their pharmacological properties [1–10]. Previously published results have shown that grapewines synthesize antimicrobial compounds in response to fungal infection. These compounds, which are referred to as phytoalexins, belong to the family of stilbenes [11–14]. Taking into regard the biological properties of (E)-stilbenols, the synthesis and antimicrobial activity of (E)-acetoxystilbenes [15] and (E)-azastilbenols and their derivatives have been studied previously in our laboratory [16–18]. In view of the fact that the substitution of acetyl group with hydroxy substituent of (E)-stilbenols, as well as that the N-substititution of benzyl and haloalkyl group with annular nitrogen atom of (E)-azastilbenols influences the antimicrobial activity, it may be of interest to direct further synthetic work towards new, yet undescribed (E)-4-[piperidino-(4`-methylpiperidino-, morpholino-) N-alkoxy] stilbenes **3a-3n**, **5a-5g**. It ought to be pointed out that on the other hand N-substituted derivatives of piperidine and morpholine showed a rather significant antimicrobial activity [19–24].

The purpose of this investigation was to elucidate the influence of the presence of the piperidine, 4-methylpiperidine, and morpholine ring, and the effect of the length of the alkyloxy bridge between the (E)-stilbene skeletone and piperidine (4`-methylpiperidine, morpholine) ring on the antimicrobial activity of **3a-3n** and **5a-5g** in order to acquire information on the structural characteristic enhancing this activity. This paper presents the synthesis and characteristics of twenty-one new (E)-4-(piperidino-N-alkoxy)stilbenes **3a-3g**, (E)-4-(4`-methylpiperidino-N-alkoxy) stilbenes **3h-3n**, (E)-4-(morpholino-N-alkoxy) stilbenes **5a-5g** and the in vitro estimation of their antimicrobial activity against such microorganismus as Gram-positive and Gram-negative bacteria, yeast, dermatophytes and moulds.

## 2. Chemistry

The synthetic approach to obtaining (E)-4-(piperidino-N-alkoxy-)stilbenes **3a-3g**, (E)-4-(4`-methylpiperidino-N-alkoxy-) stilbenes **3h-3n**, and (E)-4-(morpholino-N-alkoxy-) stilbenes **5a-5g** followed the reactions shown in Scheme 1. We accomplished the synthesis of these compounds by the reaction of the respective (E)-4-(bromoalkoxy) stilbenes **1a-1g** with piperidine

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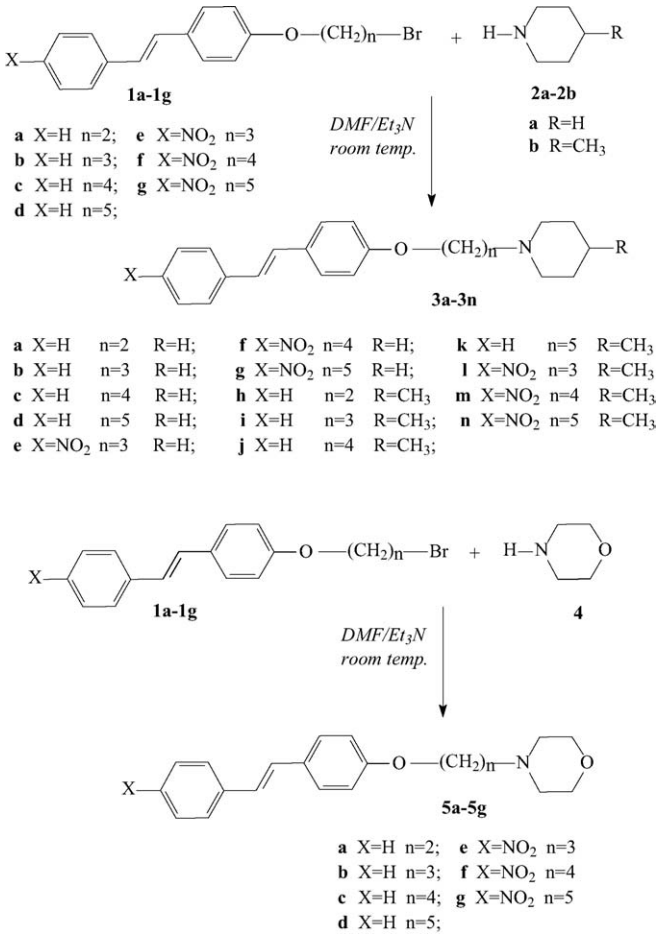



Scheme 1. Scheme of synthesis and structure of compounds **1a-1g**, **2a-2b**, **3a-3n**, **4** and **5a-5g**.

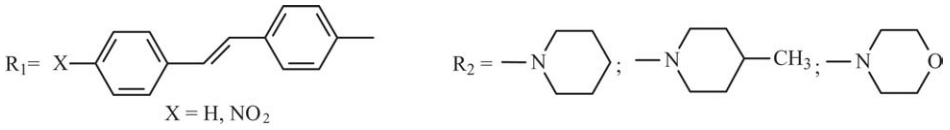
**2a** (or 4`-methylpiperidine **2b**, and morpholine **4**) in DMF in the presence of triethylamine at room temperature. By manipulating the reaction time, it was found that after 10-25 hours **3a-3n** and **5a-5g** were the predominant products. (E)-4-(bromoalkoxy-)stilbenes **1a-1g** were prepared according to a previously described procedure [25] by reacting equimolar amounts of the respective (E)-stilbenol-4, [(E)-4`-nitrostilbenol-4] and a proper dibromoalkane (1,2-dibromoethane; 1,3-dibromopropane; 1,4-dibromobutane; 1,5-dibromopentane) in 0.3 M NaOH solution of DMSO at room temperature. The structures of all new compounds obtained were determined by examining their UV/VIS, IR, $^{1}$H NMR and $^{13}$C NMR spectra as well as on the basis of elemental analyses (Tables 1–5). Assignments of the $^{1}$H NMR and $^{13}$C NMR resonances of these compounds were deduced on the basis of the signal multiplicities, and by the concerted application of the two-dimensional NMR technique HETCOR. The HETCOR results allow unequivocal assignment of the $^{13}$C NMR spectra proposed on the basis of chemical shift theory, additivity rules and by comparing the measured and calculated chemical shifts. (E) configuration in the stilbene part of the molecules of **3a-3n** and **5a-5g** was determined on the basis of their UV/VIS and IR spectra. It has been pointed out that in the UV/VIS spectra of **3a-3h** $\lambda_{max}$ are in the range 321-381 nm, as well as in the spectra of **5a-5g**, $\lambda_{max}$ in the range 321-379 nm (Table 1). According to literature [26–28] (E)-stilbenes exhibit the values of $\lambda_{max}$ in the range 290-360 nm, and for (Z)-stilbenes the values of $\lambda_{max}$ are in the range 260-280 nm. The infrared spectra of **3a-3h** and **5a-5g** show a strong band in the range 964-970 cm$^{-1}$ which, according to literature [29,30], can be attributed to the out-of-plane deformation vibration of the C-H bond of the (E)-ethy-

Table 1
Chemical and physical data of compounds **3a-3n** and **5a-5g**

| Compd. | Yield [%] | M.p. [°C] | TLC [$R_f$] | IR (KBr) [cm$^{-1}$] CH=CH | UV/VIS $\lambda_{max}$ (lg ε) | Anal |
|---|---|---|---|---|---|---|
| 3a | 78 | 80-2 | 0.57[a] | 967 | 321 (4.47) | ($C_{21}H_{25}NO$) C, H, N |
| 3b | 78 | 108-9 | 0.32[a] | 967 | 321 (4.46) | ($C_{22}H_{27}NO$) C, H, N |
| 3c | 76 | 87-90 | 0.24[a] | 969 | 321 (4.47) | ($C_{23}H_{29}NO$) C, H, N |
| 3d | 72 | 82-3 | 0.21[a] | 966 | 322 (4.44) | ($C_{24}H_{31}NO$) C, H, N |
| 3e | 42 | 50-2 | 0.30[a] | 966 | 377 (4.40) | ($C_{22}H_{26}N_2O_3$) C, H, N |
| 3f | 59 | 75-8 | 0.24[a] | 967 | 375 (4.41) | ($C_{23}H_{28}N_2O_3$) C, H, N |
| 3g | 56 | 83-6 | 0.22[a] | 963 | 378 (4.35) | ($C_{24}H_{30}N_2O_3$) C, H, N |
| 3h | 25 | 73-4 | 0.71[b] | 966 | 321 (4.46) | ($C_{22}H_{27}NO$) C, H, N |
| 3i | 13 | 73-5 | 0.67[b] | 967 | 321 (4.39) | ($C_{23}H_{29}NO$) C, H, N |
| 3j | 21 | 75-7 | 0.68[b] | 967 | 321 (4.37) | ($C_{24}H_{31}NO$) C, H, N |
| 3k | 27 | 82-3 | 0.69[b] | 966 | 321 (4.43) | ($C_{25}H_{33}NO$) C, H, N |
| 3l | 65 | 86-8 | 0.51[b] | 967 | 378 (4.51) | ($C_{23}H_{28}N_2O_3$) C, H, N |
| 3m | 40 | 78-80 | 0.50[b] | 968 | 379 (4.20) | ($C_{24}H_{30}N_2O_3$) C, H, N |
| 3n | 42 | 79-80 | 0.43[b] | 968 | 381 (4.41) | ($C_{25}H_{32}N_2O_3$) C, H, N |
| 5a | 58 | 108-110 | 0.74[a] | 968 | 321 (4.45) | ($C_{20}H_{23}NO_2$) C, H, N |
| 5b | 56 | 100-1 | 0.74[a] | 968 | 322 (4.46) | ($C_{21}H_{25}NO_2$) C, H, N |
| 5c | 75 | 59-61 | 0.75[a] | 964 | 322 (4.47) | ($C_{22}H_{27}NO_2$) C, H, N |
| 5d | 49 | 74-8 | 0.76[a] | 966 | 321 (4.42) | ($C_{23}H_{29}NO_2$) C, H, N |
| 5e | 55 | 45-8 | 0.77[a] | 971 | 378 (4.42) | ($C_{21}H_{24}N_2O_4$) C, H, N |
| 5f | 38 | 85-7 | 0.77[a] | 967 | 379 (4.41) | ($C_{22}H_{26}N_2O_4$) C, H, N |
| 5g | 56 | 69-71 | 0.76[a] | 970 | 379 (4.42) | ($C_{23}H_{28}N_2O_4$) C, H, N |

[a] $CH_3OH$: $CHCl_3$ (3:1).
[b] $CH_3OH$: $CHCl_3$ (1:5).

Table 2
$^1$H NMR data of compounds **3a-3n** and **5a-5g**



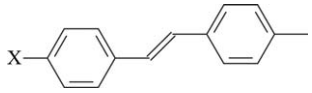

| Compd | $t_1$ | $t_2$ | $t_3$ | $t_4$ | $k_1$ | $k_2$ | $k_3$ | $k_4$ | $k_5$ | $q_1$ | $q_2$ | d | Ar, m  |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3a | 4.13 | 2.79 | 2.52 | – | – | – | – | 1.61 | 1.45 | – | – | – | 6.87–7.50 |
| 3h | 4.12 | 2.79 | 2.96 | – | – | – | – | – | – | 1.64 | 1.29 | 0.92 | 6.87–7.49 |
| 5a | 4.13 | 2.81 | 2.59 | 3.74 | – | – | – | – | – | – | – | – | 6.87–7.50 |
| 3b | 4.00 | 2.10 | 2.47 | – | 2.00 | – | – | 1.60 | 1.45 | – | – | – | 6.86–7.49 |
| 3e | 4.03 | 2.45 | 2.53 | – | 2.04 | – | – | 1.60 | 1.44 | – | – | – | 6.94–8.20 |
| 3i | 4.00 | 2.53 | 2.96 | – | 2.00 | – | – | – | – | 1.66 | 1.29 | 0.93 | 6.86–7.48 |
| 3l | 4.00 | 2.47 | 2.93 | – | 1.97 | – | – | – | – | 1.61 | 1.25 | 0.95 | 6.90–8.20 |
| 5b | 4.00 | 2.47 | 2.53 | 3.72 | 1.98 | – | – | – | – | – | – | – | 6.86–7.49 |
| 5e | 4.06 | 2.49 | 2.53 | 3.76 | 1.99 | – | – | – | – | – | – | – | 6.90–8.20 |
| 3c | 3.99 | 2.39 | 2.42 | – | 2.00 | 1.88 | – | 1.62 | 1.44 | – | – | – | 6.86–7.50 |
| 3f | 4.04 | 2.39 | 2.42 | – | 2.00 | 1.87 | – | 1.61 | 1.46 | – | – | – | 6.83–8.21 |
| 3j | 3.98 | 2.42 | 2.96 | – | 1.97 | 1.77 | – | – | – | 1.65 | 1.32 | 0.93 | 6.85–7.49 |
| 3m | 4.00 | 2.40 | 2.91 | – | 1.94 | 1.78 | – | – | – | 1.66 | 1.25 | 0.92 | 6.89–8.20 |
| 5c | 4.00 | 2.42 | 2.49 | 3.76 | 1.96 | 1.83 | – | – | – | – | – | – | 6.86–7.50 |
| 5f | 4.02 | 2.48 | 2.50 | 3.75 | 1.99 | 1.82 | – | – | – | – | – | – | 6.84–8.29 |
| 3d | 3.97 | 2.38 | 2.29 | – | 1.90 | 1.77 | 1.46 | 1.57 | 1.43 | – | – | – | 6.47–7.50 |
| 3g | 4.03 | 2.45 | 2.90 | – | 1.87 | 1.79 | 1.45 | 1.56 | 1.43 | – | – | – | 6.68–8.50 |
| 3k | 3.96 | 2.34 | 2.90 | – | 1.90 | 1.80 | 1.46 | 1.28 | – | 1.59 | 1.28 | 0.91 | 6.85–7.72 |
| 3n | 3.98 | 2.32 | 2.91 | – | 1.88 | 1.84 | 1.46 | 1.22 | – | 1.59 | 1.30 | 0.92 | 6.88–8.21 |
| 5d | 3.95 | 2.43 | 2.35 | 3.71 | 1.80 | 1.80 | 1.52 | – | – | – | – | – | 6.80–7.49 |
| 5g | 3.99 | 2.47 | 2.35 | 3.73 | 1.84 | 1.84 | 1.54 | – | – | – | – | – | 6.89–8.20 |

Table 3
$^{13}$C NMR data of **3a-3g**

| Carbon atom | Compd | | | | | | |
|---|---|---|---|---|---|---|---|
| | 3a | 3b | 3c | 3d | 3e | 3f | 3g |
| C-1 | 137.56 | 137.58 | 137.60 | 137.70 | 144.29 | 144.36 | 144.13 |
| C-2,6 | 127.09 | 126.40 | 127.00 | 127.47 | 128.36 | 128.39 | 128.28 |
| C-3,5 | 128.53 | 128.52 | 128.53 | 128.62 | 124.08 | 124.11 | 123.98 |
| C-4 | 127.58 | 127.07 | 127.00 | 127.15 | 146.37 | 146.41 | 146.13 |
| C-α | 126.15 | 126.13 | 126.14 | 126.23 | 123.93 | 123.95 | 123.98 |
| C-α’ | 127.70 | 127.57 | 127.59 | 127.68 | 132.93 | 133.00 | 132.74 |
| C-1’ | 130.08 | 129.91 | 129.94 | 129.95 | 128.81 | 128.80 | 128.84 |
| C-2’,6’ | 128.13 | 128.14 | 128.20 | 128.19 | 126.42 | 126.46 | 126.34 |
| C-3’,5’ | 114.76 | 114.67 | 114.70 | 114.89 | 114.87 | 114.89 | 114.68 |
| C-4’ | 158.47 | 158.66 | 158.66 | 158.87 | 159.25 | 159.80 | 159.35 |
| C-I | 66.09 | 66.62 | 66.06 | 67.88 | 68.80 | 67.87 | 67.78 |
| C-II | 57.96 | 56.01 | 56.00 | 59.40 | 55.73 | 58.90 | 57.00 |
| C-III | – | 26.92 | 27.20 | 26.66 | 26.50 | 27.30 | 28.66 |
| C-IV | – | – | 23.00 | 24.18 | – | 23.28 | 23.55 |
| C-V | – | – | – | 29.17 | – | – | 28.60 |
| C-VI,X | 55.12 | 54.70 | 54.58 | 54.63 | 54.45 | 54.49 | 52.87 |
| C-VII,IX | 26.04 | 26.06 | 25.91 | 25.93 | 25.60 | 25.76 | 23.62 |
| C-VIII | 24.28 | 24.52 | 24.46 | 24.44 | 24.20 | 24.30 | 23.55 |

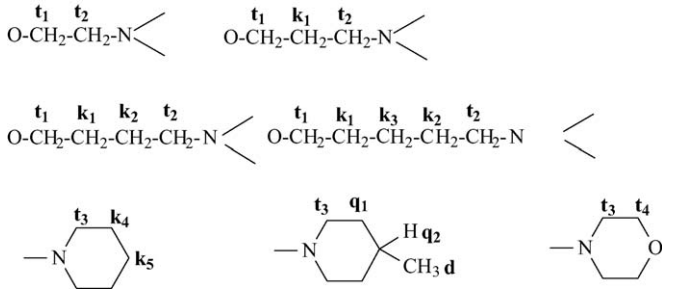
lene bridge of the stilbene skeletone (Table 1). In the $^1$H NMR spectra of **3a-3n** and **5a-5g** there are two triplets of O-$CH_2$ ($t_1$) and N-$CH_2$ ($t_2$) protons of N-alkoxy chain linking (E)-stilbene and piperidine (4-methylpiperidine, morpholine) rings. The values of the chemical shifts of the signals of these protons were established in the range 3.95-4.06 δ and 2.39-2.81 δ, respectively (Scheme 2, Table 2). The $^1$H NMR spectra of **3a-3g** show two quintets ($k_4$ and $k_5$) of protons of methylene groups of piperidine ring (Scheme 2, Table 2). The values of the chemical shifts of the signals of these protons fall in the range 1.56-1.62 δ and 1.43-1.46 δ, respectively. The presence of these signals in the $^1$H NMR spectra of **3a-3g** indicates the occurrence of the piperidine ring in the molecules of these compounds. The $^1$H NMR spectra of **3h-3n** show a dublet of

Table 4
$^{13}$C NMR data of **3h-3n**

| Carbon atom | Compd | | | | | | |
|---|---|---|---|---|---|---|---|
| | 3 h | 3i | 3j | 3k | 3l | 3m | 3n |
| C-1 | 137.58 | 137.47 | 137.51 | 137.61 | 144.23 | 144.27 | 144.28 |
| C-2,6 | 127.15 | 127.02 | 127.03 | 127.11 | 128.36 | 128.35 | 128.35 |
| C-3,5 | 128.59 | 128.47 | 128.49 | 128.58 | 124.11 | 124.08 | 124.08 |
| C-4 | 127.64 | 127.52 | 127.55 | 127.63 | 146.34 | 146.27 | 146.27 |
| C-α | 126.19 | 126.07 | 126.09 | 126.17 | 129.81 | 123.84 | 123.82 |
| C-α’ | 127.82 | 128.64 | 127.35 | 128.58 | 132.82 | 132.91 | 132.92 |
| C-1’ | 130.09 | 129.84 | 129.84 | 129.89 | 129.03 | 130.84 | 128.65 |
| C-2’,6’ | 128.14 | 128.08 | 128.11 | 128.20 | 128.77 | 128.74 | 126.40 |
| C-3’,5’ | 114.89 | 114.59 | 114.57 | 114.60 | 115.06 | 114.78 | 114.77 |
| C-4’ | 158.47 | 158.52 | 158.57 | 158.76 | 159.19 | 159.68 | 159.74 |
| C-I | 66.16 | 66.43 | 67.71 | 67.79 | 68.81 | 67.71 | 67.86 |
| C-II | 57.49 | 55.58 | 58.93 | 58.97 | 55.54 | 58.54 | 59.03 |
| C-III | – | 26.85 | 27.41 | 26.74 | 26.74 | 27.29 | 26.24 |
| C-IV | – | – | 23.45 | 24.16 | – | 23.47 | 24.15 |
| C-V | – | – | – | 29.14 | – | – | 29.10 |
| C-VI,X | 54.48 | 54.09 | 54.90 | 54.02 | 54.07 | 53.93 | 54.10 |
| C-VII,IX | 34.19 | 34.19 | 34.13 | 34.22 | 34.17 | 34.29 | 34.32 |
| C-VIII | 30.52 | 30.79 | 30.79 | 30.76 | 30.78 | 30.71 | 30.81 |
| C-XI | 21.86 | 21.89 | 21.87 | 21.87 | 21.89 | 21.83 | 21.89 |

Table 5
$^{13}$C NMR data of **5a-5g**

| Carbon atom | Compd | | | | | | |
|---|---|---|---|---|---|---|---|
| | 5a | 5b | 5c | 5d | 5e | 5f | 5g |
| C-1 | 137.64 | 137.53 | 137.52 | 137.46 | 144.27 | 144.13 | 144.30 |
| C-2,6 | 127.25 | 126.49 | 126.45 | 126.32 | 128.37 | 128.27 | 128.33 |
| C-3,5 | 128.66 | 128.53 | 128.53 | 128.48 | 124.00 | 124.01 | 124.10 |
| C-4 | 127.72 | 127.11 | 127.10 | 127.03 | 146.40 | 146.18 | 146.40 |
| C-α | 126.27 | 126.14 | 126.13 | 126.04 | 124.09 | 123.85 | 123.96 |
| C-α’ | 127.27 | 127.59 | 127.59 | 127.54 | 132.90 | 132.77 | 132.94 |
| C-1’ | 130.38 | 130.01 | 129.96 | 129.80 | 128.89 | 128.69 | 128.80 |
| C-2’,6’ | 128.16 | 128.11 | 128.11 | 128.06 | 128.37 | 126.34 | 126.44 |
| C-3’,5’ | 114.84 | 114.64 | 114.59 | 114.51 | 114.87 | 114.71 | 114.84 |
| C-4’ | 158.47 | 158.57 | 158.55 | 158.57 | 159.70 | 159.47 | 159.78 |
| C-I | 66.69 | 67.02 | 67.66 | 67.74 | 68.81 | 67.66 | 67.86 |
| C-II | 57.42 | 55.58 | 58.59 | 58.94 | 55.41 | 58.51 | 58.88 |
| C-III | – | 26.56 | 27.23 | 26.31 | 26.34 | 27.13 | 26.18 |
| C-IV | – | – | 23.03 | 24.02 | – | 22.95 | 23.91 |
| C-V | – | – | – | 29.18 | – | – | 29.04 |
| C-VI,X | 54.10 | 53.80 | 53.64 | 53.75 | 53.70 | 53.58 | 53.72 |
| C-VII,IX | 65.94 | 66.19 | 66.81 | 66.92 | 66.92 | 66.73 | 66.89 |



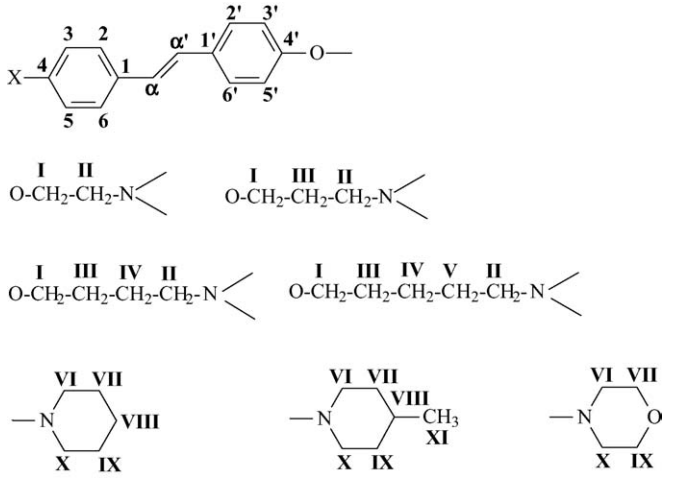

Scheme 2. The numbering of protons of N-alkoxypiperidine, N-alkoxy-4-methylpiperidine and N-alkoxymorpholine groups of **3a-3n**; **5a-5g**.

protons of a methyl group in the range 0.91-0.95 δ. The presence of this signal in the $^1$H NMR spectra of **3h-3n** proves the occurrence of the 4-methylpiperidine ring in the molecules of these compounds. The $^1$H NMR spectra of **5a-5g** in the range of 3.71-3.75 δ show a triplet of proton signals of O-$CH_2$ groups of morpholine ring. These signals indicate the occurrence of the morpholine ring in the investigated molecules (Scheme 2, Table 2).

The presence of piperidine (4-methylpiperidine, morpholine) ring in the molecules of **3a-3n** and **5a-5g** is also indicated in the $^{13}$C NMR spectra of these compounds (carbons VI, X; VII, IX and VIII - Tables 3–5).

## 3. Biology

New (E)-4-[piperidino-]N-alkoxystilbenes **3a-3g**, (E)-4-[4`-methylpiperidino-]N-alkoxystilbenes **3h-3n** and (E)-4-[morpholino-]N-alkoxystilbenes **5a-5g** were tested in vitro in order to evaluate their antimicrobial effect. The potential antimicrobial activity of compounds **3a-3n** and **5a-5g** was estimated in vitro by determining the MIC against a wide spectrum of microorganism: Gram-positive cocci (*Staphylococcus aureous*



Scheme 3. The numbering of carbons of (E)-stilbene, N-alkoxypiperidine, N-alkoxy-4-methylpiperidine and N-alkoxymorpholine groups of **3a**-**3n**; **5a**-**5g**.

*209P FDA, Streptococcus faecalis ATCC 8040*), aerobic bacilli (*Bacillus subtilis ATCC 1633*), Gram-negative rods (*Escherichia coli PZH 026 B6, Klebsiella pneumoniae 231, Pseudomonas aeruginosa SR1*), yeasts (*Candida albicans PCM 1409 PZH*) dermatophytes (*Microsporum Gypseum K1*), moulds *(Aspergillus fumigatus C1*) (Scheme 3).

## 4. Results

Table 6 lists the antimicrobial susceptibility results against Gram-positive cocci, aerobic bacilli, Gram-negative rods, yeast, dermatophytes and moulds. (E)-4-[piperidino-N-ethoxy-]stilbene **3a**, (E)-4-[piperidino-N-propioxy-]stilbene **3b**, (E)-4-[piperidino-N-butoxy-]stilbene **3c**, (E)-4-[piperidino-N-butoxy-]4`-nitrostilbene **3f**, (E)-4-[piperidino-N-pentoxy-]4`-nitrostilbene **3g**, (E)-4-[4`-methylpiperidino-N-ethoxy-]stilbene **3h**, (E)-4-[4`-methylpiperidino-N-pentoxy-]stilbene **3k**, (E)-4-[4`-methylpiperidino-N-propioxy-]4`-nitrostilbene **3l**, (E)-4-[4`-methylpiperidino-N-butoxy-]4`-nitrostilbene **3m** and (E)-4-[4`-methylpiperidino-N-pentoxy-]4`-nitrostilbene **3n** tested in this study exhibited considerable antimicrobial activity against Gram-positive cocci *Staphylococcus aureus*. (E)-4-[4`-methylpiperidino-N-ethoxy-]stilbene **3h**, (E)-4-[4`-methylpiperidino-N-pentoxy-]4`-nitrostilbene **3n** exhibited also a high activity against *Streptococcus feacalis* and aerobic bacilli- *Bacillus subtilis*. (E)-4-[4`-methylpiperidino-N-pentoxy-]stilbene **3k** and (E)-4-[4`-methylpiperidino-N-butoxy-]4`-nitrostilbene **3m** showed considerable antibacterial activity agaist *Bacilus subtilis*. Compounds **3d**, **3e**, were endowed with a medium activity against cocci *Staphylococcus aureous, Streptococcus faecalis* as well as *Bacillus subtilis.* A medium activity against, *Streptococcus faecalis* and *Bacillus subtilis* was exhibited also by **3a**, **3e**, **3f**, **3g** and **3l**. Coumpound **3a** was also endowed with a medium activity against Gram-negative rods- *Escherichia coli*. (E)-4-[morpholino-N-butoxy-]stilbene **5c**, (E)-4-[morpholino-N-pentoxy-]stilbene **5d**, (E)-4-[morpholino-N-propioxy-]4`-nitrostilbene **5e**, (E)-4-[morpholino-N-butoxy-]4`-nitrostilbene **5f** and (E)-4-[morpholino-N-pentoxy-]4`-nitrostilbene **5g** were endowed only with medium antimicrobial activity against Gram-positive cocci- *Staphylococcus aureus* and moulds- *Aspergillus fumigatus*. All the compounds tested in this study displayed not significant effect against the Gram-negative rods *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, in general, MIC > 100g/cm$^3$.

Table 6
Antimicrobial activity of **3a**-**3n** and **5a**-**5g**

| Compd | Minimal inhibitory concentration (MIC) μg/cm$^3$ * | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | SA | SF | BS | EC | KP | PA | CA | MG | AF |
| 3a | 10 | 100 | 100 | 100 | – | – | 50 | – | 50 |
| 3b | 5 | – | – | – | – | – | – | – | 100 |
| 3c | 5 | 100 | 100 | – | – | – | – | – | 100 |
| 3d | 100 | 100 | 100 | – | – | – | – | – | 50 |
| 3e | 100 | 100 | 100 | – | – | – | – | – | – |
| 3f | 7.5 | 100 | 100 | – | – | – | – | – | – |
| 3g | 10 | 100 | 100 | – | – | – | – | – | 50 |
| 3h | 7.5 | 7.5 | 5 | – | – | – | 50 | – | 50 |
| 3i | – | – | – | – | – | – | 50 | – | 50 |
| 3j | – | – | – | – | – | – | 50 | – | 50 |
| 3k | 7.5 | 100 | 5 | – | – | – | 50 | – | 10 |
| 3l | 7.5 | 100 | 100 | – | – | – | – | – | 100 |
| 3m | 10 | 100 | 10 | – | – | – | 100 | – | 10 |
| 3n | 10 | 7.5 | 10 | – | – | – | – | – | 50 |
| 5a | – | – | – | – | – | – | – | – | – |
| 5b | – | – | – | – | – | – | – | – | – |
| 5c | 100 | – | – | – | – | – | – | – | 50 |
| 5d | 100 | – | – | – | – | – | – | – | 50 |
| 5e | 100 | – | – | – | – | – | – | – | 50 |
| 5f | 100 | – | – | – | – | – | – | – | 50 |
| 5g | 100 | – | – | – | – | – | – | – | 50 |
| A | 5.0 | 5.0 | 5.0 | 5.0 | 50.0 | 50.0 | – | – | – |
| B | – | – | – | – | – | – | 0.5 | 10.0 | 1.0 |

* SA: *Staphylococcus aureus 209P FDA*; CA: *Candida albicans PCM 1409 PZH*; SF: *Streptococcus faecalis ATCC 8040*; MG: *Microsporum gypseum K1*; BS: *Bacillus subtilis ATCC 1633*; AF: *Aspergillus fumigatus C1*; EC: *Escherichia coli PZH 026 B6*; A: chloroamphenicole; KP: *Klebsiella pneumoniae 231*; B: amphoterricin B; PA- *Pseudomonas aeruginosa SP1*; – Not tested because MIC value is higher than 100 μg/cm$^3$.

The newly synthesised compounds (E)-[4`-metylpiperidino-N-pentoxy-]stilbene **3k** and (E)-4-[4`-methylpiperidino-N-butoxy-]stilbene **3m** showed good antimicrobial properties against moulds- *Aspergillus fumigatus*. The compounds **3a**, **3b**, **3c**, **3d**, **3g**, **3h**, **3i, 3j**, **3l** and **3n** as well as **5a**-**5g** showed a medium activity against *Aspergillus fumigatus*. Additionally, a medium activity against yeast- *Candida albicans* was exhibited by compounds **3a**, **3 h**, **3i**, **3j**, **3k** and **3m**. It is noteworthy that **3a** displayed a wide spectrum of antimicrobial activity against 6 strains (SA, SF, BS, EC, CA, CF – Table 6) as well as **3h**, **3k**, and **3m** against 5 strains (SA, SF, BS, EC, AF-Table 6).

## 5. Discussion

This work presents a novel class of potent, wide-spectrum antimicrobial compounds. The results are worth noting because in recent years increasing rates of antimicrobial resistance among community and nosocomial pathogenes has severely limited the therapeutic options for treating infections caused by such organisms. From among the compounds tested **3h**, **3k** and **3m** proved to be the most effective.

As regards the structure-activity relationship of the substituted derivatives of (E)-stilbenol-4 and (E)-4`-nitrostilbenol-4, the introduction of 4-alkoxy-N-piperidine group and 4-alkoxy-N-4`-methylpiperidine group as substitutent in the para position of the (E)-stilbene [(E)-4`-nitrostilbene] moiety noticeably enhanced the antibacterial activity displayed by the unsubstituted stilbenols [15]. The introduction of 4-alkoxy-N-morpholine group as substituent in the para position of the (E)-stilbene [(E)-4`-nitrostilbene] moiety did not noticeably enhance the antimicrobial activity displayed by the unsubstituted stilbenols [15]. (E)-4-(piperidino-N-propioxy-]stilbene **3b** and (E)-[piperidino-N-butoxy-]stilbene **3c** displayed the antibacterial activity against *Staphylococcus aureus* comparative to that of the reference drug chloramphenicol (Table 6). (E)-4-[4`-methylpiperidino-N-pentoxy-]stilbene **3k** and (E)-4-[4`-methylpiperidino-N-ethoxy-]stilbene **3h** displayed the same antibacterial activity against *Bacillus subtilis* similar to that of the reference drug chloramphenicol (Table 6).

In conclusion, taking into account that **3a, 3h**, **3k** and **3m** are wide spectrum antimicrobial substances, it can be concluded that they are promising new agents for treatment of microbial infections.

## 6. Experimental

### 6.1. Chemistry

The purity of all described compounds was checked by m. p.'s TLC and elemental analysis. Melting points (uncorrected) were determined on Böetius microscope hot stage. $R_f$ values refer to TLC silica gel $F_{254}$ TLC plates (Merck) developed with $CHCl_3$ : MeOH (5:1) and observed under UV light (λ=254 and 366 nm). UV/VIS spectra were recorded with a Specord UV/VIS spectrophotometer in $CHCl_3$. IR spectra were recorded with a FTIR Bruker IFS-113 V spectrophotometer in KBr pellets. The $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were recorded on a Varian Mercury Spectrometer operating at 300.07 MHz (proton) or 75.46 mHz (carbon). The data were obtained from $CDCl_3$ solutions. The chemical shifts were referenced to tetramethylsilane. Chemical shifts are given in the δ scale (ppm) and coupling constants in Hz. $^1$H NMR (300.07) spectra were recorded with spectral width 9 KHz, acquisition time 2.0 s, pulse width 6 μs and double precision acquisition time. $^{13}$C NMR (75.460 MHz) spectra were recorded with spectral width 18.76 KHz, acquisition time 1.0 s, recycle delay 1.0 s and pulse width 15 μs. Heteronuclear 2D$^{13}$C NMR – $^1$H NMR chemical shift correlation experiments were carried out using HETCOR spectra. The spectra were acquired with 2K data points, 256 increments and spectral width 19.63 KHz for $^{13}$C and 4.97 KHz for $^1$H. Elemental analyses were performed with a Vector Euro EA 3000 Analyzer.

(E)-4-bromoethoxystilbene **1a** [31], (E)-4-bromopropioxystilbene **1b** [31], (E)-bromobutoxystilbene **1c** [25], (E)-4-bromopentoxystilbene **1d** [25], (E)-4`-nitro-4-bromopropioxystilbene **1e** [25], (E)-4`-nitro-4-bromobutoxystilbene **1f** [25], (E)-4`-nitro-4-bromopentoxystilbene **1g** [25], were obtained according to literature. Piperidine, 4-methylpiperidine and morpholine were purchased from Aldrich.

*General procedure for the synthesis of compounds* **3a-3n** and **5a-5g**.

To a solution of the corresponding (E)-4-bromoalkoxystilbene **1a-1g** (1 mmol) in DMF (70 ml) triethylamine (8 mmol) and piperidine (4`-methylpiperidine, or morpholine) (1 mmol) were added on constant stirring. After stirring for 10-25 h (i.e. **3a**, **3b**, **5a**, **5b** – 25 h; **3c**,**3f** – 24 h; **3g**, **5e**, **5f**, **5g** – 21 h, **3d**, **3i**, **3e**, **5c**, **5d** – 18 h; **3h**, **3k** – 15 h; **3m**, **3j** – 11 h; **3h**, **3l** – 10 h) at room temperature, distilled water (60 ml) was added to the reaction mixture. The precipitated solids of **3a-3n** and **5a-5g** were then filtered off, dried and recrystallized from DMF: $H_2O$ (3:2).

### 6.2. Microbiology

#### 6.2.2. Determination of minimum inhibitory concentration (MIC)

The microorganisms used were supplied by – National Institute of Hygiene in Warsaw (*Staphylococcus aureus 209P FDA*, *Escherichia coli PZH 026 B6*, *Candida albicans PCM 1409 PZH*), American type Culture Collection (*Streptococcus faecalis ATCC 8040*, *Bacillus subtilis ATCC* 1633), Department of Microbiology, Poznań University of Medical Sciences (*Klebsiella pneumoniae 231*, *Pseudomonas aeruginosa SP1*), Department of Medical Mycology, Poznań University of Medical Sciences (*Aspergillus fumigatus C1*, *Microsporum gypseum K1*).

The compounds were dissolved using DMSO (Serva); to form solutions of the concentration 1000 μg/cm$^3$. A series of dilutions with concentrations ranging form 10 to 1000 μg/cm$^3$ were prepared for each compound.

The MIC values of the compounds were determined, with reference to standard microorganisms, by introducing 1 cm$^3$ of the corresponding solutions at various concentrations into a series of tubes (each 12×100 mm), 0.1 cm$^3$ of a standarized 1:1000 diluted suspension of a microorganism was added. The MIC values were determined after 18 hours of incubation at 37°C. Penassay Broth (Difco) was used as the test medium for bacteria; in all assays both bacterial culture sterility and standard bacterial growth were checked. Sabouraud dextrise broth (Difco) was used as a test medium for fungi; MIC values were determined after 3-7 days of incubation at 25°C. In all assay both fungi culture sterility and standard fungi growth were checked. The MIC values determined were compared with those of the standards, chloramphenicol (the reference bactericidal drug) and amphotericine B (the reference antifungal drug). The results are listed in Table 6.

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