REACTION OF HYDRAZIDE OF (TETRAZOL-5-YL)ACETIC ACID WITH ISOTHIOCYANATES AND ANTIMICROBIAL INVESTIGATIONS OF NEWLY-OBTAINED COMPOUNDS

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Abstract - In the reaction of hydrazide of (tetrazol-5-yl)acetic acid (1) with isothiocyanate the respective thiosemicarbazide derivatives 2 were obtained. Further cyclization with 2% NaOH led to the formation of 3-[(tetrazol-5-yl)-methyl]-4-substituted-1,2,4-triazoline-5-thione 3. The structures of all new products were confirmed by analytical and spectroscopic methods. Five compounds were screened for their in vitro activity against some species of aerobic bacteria and fungi. Derivatives of 1,2,4-triazoline-5-thione can exist in two major tautomeric forms; thiole and thione. We have established experimentally that all obtained compounds 3, were in the thione form. Geometry optimization of tautomeric forms of 3c and 3f was carried out.

INTRODUCTION

Searching for new chemical compounds possessing certain pharmacological activity is a basic task of present-day chemistry. In the last few decades, the chemistry of 1,2,4-triazole derivatives has received considerable attention because of their synthetic and biological importance. They have been reported to associate with antimicrobial, fungicidal, anti-inflammatory, antiparasitic, insecticidal, herbicidal, antiviral, antitumor, anticonvulsant, antidepressant, hypotensive effects and plant growth regulatory activities.1-8 Furthermore, tetrazole moiety is a structural element of drugs that have antimicrobial activity such as Cefazolin, Cefamandol, and Cefaperazol. The development of novel synthetic strategies for obtaining compounds containing the 1,2,4-triazole system has been the subject of our research for the past few years.9-15 Encouraged by observations that the combination of two or more heterocyclic and non-
heterocyclic systems frequently substantially enhances biological profile,\textsuperscript{16-17} we have synthesized novel compounds containing (tetrazol-5-yl)methyl fragment at the position 3 of the 4-substituted-1,2,4-triazoline-5-thione derivatives. Herein, we present a study on some new 1,2,4-triazoline-5-thione derivatives that were expected to exhibit promising pharmacological activity.

**RESULTS AND DISCUSSION**

We have used (tetrazol-5-yl)acetic acid hydrazide\textsuperscript{(1)} as the starting material for synthesis of new derivatives of 1,2,4-triazoline-5-thione. It was obtained in the reaction of ethyl (tetrazol-5-yl)acetate with 80% hydrazine hydrate. New thiosemicarbazide derivatives \textsuperscript{2} were obtained by the reaction of \textsuperscript{1} with isothiocyanates. The conditions of the reaction were established experimentally. Thiosemicarbazides \textsuperscript{2} were subjected to cyclization in 2\% solution of sodium hydroxide yielding corresponding, 3-([(tetrazol-5-yl)methyl]-4-substituted-1,2,4-triazoline-5-thione \textsuperscript{3}. The reactions were performed according to the Scheme 1:

\[
\begin{array}{c}
\text{N-N} \\
\text{H} \\
\text{CH}_2 \text{C-} \text{NHNH}_2 \\
\text{RNCS} \\
\text{N-N} \\
\text{H} \\
\end{array}
\xrightarrow{2\% \text{NaOH}}
\begin{array}{c}
\text{N-N} \\
\text{H} \\
\text{CH}_2 \text{C-} \text{NHNH-C-NHR} \\
\text{N} \\
\end{array}
\text{2a - 2f}
\]

\[
\begin{array}{c}
\text{N-N} \\
\text{H} \\
\text{CH}_2 \text{C-} \text{NHNH-C-NHR} \\
\text{N} \\
\text{R} \\
\text{SH} \\
\end{array}
\xrightarrow{2\% \text{NaOH}}
\begin{array}{c}
\text{N-N} \\
\text{H} \\
\text{CH}_2 \text{C-} \text{NH-C-S} \\
\text{N} \\
\text{R} \\
\end{array}
\text{3a - 3f}
\]

The structure of the obtained products was confirmed by the elemental analysis as well as by the IR and \textsuperscript{1}H NMR spectra and in a few cases by the \textsuperscript{13}C NMR spectra. Substituents and corresponding yields of intermediates (\textsuperscript{2}) and products (\textsuperscript{3}) are collected in Tables 1 and 2. As indicated in Scheme 1, products of the cyclization can exist in two major tautomeric forms; thiole (the structure on the left) and thione. We have established experimentally that all obtained compounds (3), were in the thione form.

The results of antibacterial and antifungal in vitro activity of the five of newly synthesized compounds (\textsuperscript{2c, 2d, 2f, 3c, 3f}) obtained using the agar dilution method did not show very significant affect against most of the examined microorganisms. It was found that the tested compounds were not active against all Gram-negative bacteria (MIC $\geq$500 mg L\textsuperscript{-1}) and the majority of Gram-positive bacteria (MIC $\geq$500 mg L\textsuperscript{-1}), except for the compound \textsuperscript{2d}. This compound affected the growth of *Bacillus subtilis* with MIC = 250 mg L\textsuperscript{-1} and showed promising activity against *Micrococcus luteus* ATCC 10240 with MIC = 125 mg L\textsuperscript{-1}. Besides, using the broth dilution method strong inhibition by about 80-90\% of
Table 1. Substituents and yields of thiosemicarbazide derivatives.

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>Yield [%]</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>79</td>
<td>C₆H₅</td>
</tr>
<tr>
<td>2b</td>
<td>80</td>
<td>4-MeC₆H₄</td>
</tr>
<tr>
<td>2c</td>
<td>80</td>
<td>4-MeOC₆H₄</td>
</tr>
<tr>
<td>2d</td>
<td>70</td>
<td>4-BrC₆H₄</td>
</tr>
<tr>
<td>2e</td>
<td>80</td>
<td>2-FC₆H₄</td>
</tr>
<tr>
<td>2f</td>
<td>68</td>
<td>CH₂C₆H₅</td>
</tr>
</tbody>
</table>

Table 2. Substituents and yields of 1,2,4-triazoline-5-thione derivatives.

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield [%]</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>78</td>
<td>C₆H₅</td>
</tr>
<tr>
<td>3b</td>
<td>77</td>
<td>4-MeC₆H₄</td>
</tr>
<tr>
<td>3c</td>
<td>80</td>
<td>4-MeOC₆H₄</td>
</tr>
<tr>
<td>3d</td>
<td>65</td>
<td>4-BrC₆H₄</td>
</tr>
<tr>
<td>3e</td>
<td>76</td>
<td>2-FC₆H₄</td>
</tr>
<tr>
<td>3f</td>
<td>62</td>
<td>CH₂C₆H₅</td>
</tr>
</tbody>
</table>

the growth of *M. luteus* ATCC 10240 was noted at lower concentrations ranging from 3.91 - 62.5 mg L⁻¹ as shown in Figure 1. It was also found that two cephalosporines - cefazolin with similar tetrazole system as the compound 2d and cefuroxime without such system, inhibited growth of *M. luteus* ATCC 10240 at much lower concentrations with MIC of 0.25 or 1.95 mg L⁻¹, respectively (Figure 1).

Furthermore, there was no essential *in vitro* antifungal activity of the five tested compounds against yeasts and moulds. Only the compounds 2d and 3f affected the growth of *Trichophyton mentagrophytes* ATCC 9533 with MIC = 250 mg L⁻¹.

In conclusion, our data suggest that the compound 2d, which has the lowest value of logP, appears to be a promising precursor of compounds with narrow spectrum, possessing the increased activity against *Micrococcus* spp. This bacterial species is generally thought to be a saprophytic or commensal microorganism, normally present in human skin microflora. However, in rare cases it was noted as an opportunistic pathogen, particularly in hosts with compromised immune systems, such as HIV patients. In immunosuppressed patients micrococci may be involved in various infections, including recurrent bacteremia, septic shock, septic arthritis, endocarditis, meningitis, and pulmonary infections.¹⁸

We have attempted calculations of main properties of the compounds for which biological activity has been tested. However, we were unable to converge two of the acyclic structures. Thus we have restricted our calculations to two compounds 3e and 3f only. Both SH and NH tautomers were optimized. In agreement with the experiment in both cases NH tautomers are significantly more stable than the corresponding SH forms; Gibbs free energy difference between the tautomers is equal to 14.9 and 16.3 kcal/mol for 3c and 3f, respectively. Obtained values of logP absolute energies are listed in the Table 3. Optimized structures in aqueous solution of the NH tautomers are illustrated in Figure 2.

Basic geometrical parameters are not substantially perturbed by the change of the solvation model and are also quite similar for both compounds (3c and 3f), which differ mostly in the relative angles between the
Figure 1. Concentration-dependent inhibition of Micrococcus luteus ATCC 10240 growth by compound 2d, cefuroxime and cefazolin and assessed by broth dilution method.

Table 3. Gibbs free energies and logP for tautomers of 3c, 3f and 2d.

<table>
<thead>
<tr>
<th>Structure</th>
<th>logP</th>
<th>Gibbs free energy in water (a.u.)</th>
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</thead>
<tbody>
<tr>
<td>3c – SH tautomer</td>
<td>7.86</td>
<td>-1282.454275</td>
</tr>
<tr>
<td>3c – NH tautomer</td>
<td>6.87</td>
<td>-1282.477999</td>
</tr>
<tr>
<td>3f – SH tautomer</td>
<td>5.49</td>
<td>-1207.245810</td>
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<tr>
<td>3f – NH tautomer</td>
<td>5.05</td>
<td>-1207.271703</td>
</tr>
<tr>
<td>2d</td>
<td>3.67</td>
<td>-3815.543538</td>
</tr>
</tbody>
</table>

Figure 2. Optimized structures of 3c, 3f and 2d

rings. Bond lengths of the triazole ring of all structures are collected in the Table 4 and compared to the corresponding distances in 2d. The only important difference that can be noticed is change in the S-C
bond between the thiol (SH) and thione (NH) forms. The shortening of this bond on going from the double bond of the NH tautomer to the single bond in SH is about 0.07 Å. Since identification of the tautomeric forms of triazoles on the basis of spectroscopic data is still problematic this structural information may prove useful in future studies of new compounds of this class.

Table 4. Bond length of 3c, 3f and 2d (Å).

<table>
<thead>
<tr>
<th>bond</th>
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<th>3f</th>
<th>2d</th>
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<td>NHaq</td>
<td>NHoct</td>
<td>SHaq</td>
</tr>
<tr>
<td>H-S</td>
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<td>-</td>
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</tr>
<tr>
<td>S-C</td>
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</tr>
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<td>N-N</td>
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<td>1.367</td>
<td>1.387</td>
</tr>
<tr>
<td>N-C</td>
<td>1.305</td>
<td>1.306</td>
<td>1.311</td>
</tr>
<tr>
<td>C-N</td>
<td>1.385</td>
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</tr>
<tr>
<td>N-C</td>
<td>1.386</td>
<td>1.387</td>
<td>1.375</td>
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</table>

**EXPERIMENTAL**

**Chemistry**

Melting points were determined in Fisher-Johns blocks and presented are without any corrections. IR spectra were recorded in KBr using Specord IR-75 spectrophotometer. The $^1$H NMR spectra were recorded on a Brucker Avance 300 in DMSO-$d_6$ with TMS as internal standard. The $^{13}$C NMR spectra were recorded on a Brucker Avance 300 in DMSO-$d_6$ with TMS as internal standard. Chemicals were purchased from Lancaster or Merck Co. and used without further purification. Purity was checked by TLC on Merck Co. plates Aluminium oxide 60 F$_{254}$ in a CHCl$_3$/C$_2$H$_5$OH (10:1) solvent system with UV visualization.

1-[(Tetrazol-5-yl)acetyl]-4-substituted thiosemicarbazide (2a-2f)

0.01 Mol of hydrazide of (tetrazol-5-yl)acetic acid (1) and 0.01 mol of isothiocyanate was heated at the 60-70 °C for 8 h. The product was washed with Et$_2$O to remove the unreacted isothiocyanate, dried and crystallized from EtOH (68-80%). The results are collected in the Table 1.

4-Phenyl-1-[(tetrazol-5-yl)acetyl]thiosemicarbazide (2a): mp 154-156 °C. IR (cm$^{-1}$): 3240 NH; 3060 CH arom; 2970, 1432 CH aliph; 1700 C=O; 1552 C=N. $^1$H NMR (DMSO-$d_6$) δ: 3.72 (s, 2H, C$_2$H$_2$); 7.05-7.62 (m, 5H, arom); 8.66 (s, 1H, NH); 9.02; 10.12; 11.32 (3s, 3H, 3NH). Anal. Calcd for C$_{10}$H$_{11}$N$_7$OS: C 43.31, H 4.00, N 35.36. Found: C 43.22, H 4.01, N 35.33.

4-(4-Tolyl)-1-[(tetrazol-5-yl)acetyl]thiosemicarbazide (2b): mp 160-162 °C. IR (cm$^{-1}$): 3210 NH; 3071 CH arom; 2950, 1440 CH aliph; 1720 C=O; 1556 C=N. $^1$H NMR (DMSO-$d_6$) δ: 2.24 (s, 3H, CH$_3$); 7.05-7.62 (m, 4H, arom); 8.69 (s, 1H, NH); 9.62 (s, 2H, 2NH); 10.93 (s, 1H, NH). Anal. Calcd for C$_{11}$H$_{13}$N$_7$OS: C 45.35, H 4.50, N 33.65. Found: C 45.31, H 4.47, N 33.38.
4-(4-Methoxyphenyl)-1-[(tetrazol-5-yl)acetyl]thiosemicarbazide (2c): mp 205-207 °C. IR (cm⁻¹): 3200 NH; 3070 CH arom; 1700 C=O; 1548 C=N. ¹H NMR (DMSO-d₆) δ: 3.72 (s, 3H, CH₃); 7.85-7.88 (m, 4H, arom); 8.68 (s, 1H, NH); 9.58 (s, 2H, 2NH); 11.07 (s, 1H, NH). ¹³C NMR: 29.3 (CH₂); 55.2 (CH₃); 113.1, 113.4 (4x C₆H₄); 126.2, 133.3, 152.2 (3x C₆H₄); 159.4 (C=O); 166.4 (C=S). Anal. Calcd for C₁₁H₁₃N₇O₂S: C 42.99, H 4.26, N 31.90. Found: C 42.98, H 4.20, N 32.00.

4-(4-Bromophenyl)-1-[(tetrazol-5-yl)acetyl]thiosemicarbazide (2d): mp 208-210 °C. IR (cm⁻¹): 3230 NH; 3070 CH arom; 2940, 1455 CH aliph; 1690 C=O; 1545 C=N. ¹H NMR (DMSO-d₆) δ: 3.80 (s, 2H, CH₂); 7.28-7.70 (m, 4H, arom); 8.94 (s, 1H, NH); 9.84 (s, 2H, 2NH); 10.60 (s, 1H, NH). ¹³C NMR: 29.1 (CH₂); 124.5, 132.2, 138.9 (3x C₆H₄); 130.4, 130.8 (4x C₆H₄); 151.5 (C=O); 165.7 (C=S). Anal. Calcd for C₁₀H₁₀BrN₇OS: C 33.72, H 2.83, N 27.63. Found: C 33.72, H 2.85, N 27.58.

4-(2-Fluorophenyl)-1-[(tetrazol-5-yl)acetyl]thiosemicarbazide (2e): mp 164-166 °C. IR (cm⁻¹): 3240 NH; 3058 CH arom; 2940, 1468 CH aliph; 1698 C=O; 1551 C=N; 1510 C-N. ¹H NMR (DMSO-d₆) δ: 3.75 (s, 2H, CH₂); 7.12-7.52 (m, 4H, arom); 8.17 (s, 1H, NH); 8.55; 8.98; 10.07 (3s, 3H, 3NH). Anal. Calcd for C₁₀H₁₀FN₇OS: C 40.67, H 3.41, N 33.20. Found: C 40.68, H 3.20, N 33.02.

4-Benzyl-1-[(tetrazol-5-yl)acetyl]thiosemicarbazide (2f): mp 160-161 °C. IR (cm⁻¹): 3242 NH; 3070 CH aromatic; 2950, 1457 CH aliph; 1700 C=O; 1558 C=N. ¹H NMR (DMSO-d₆) δ: 3.73 (s, 2H, CH₂); 4.73 (s, 2H, CH₂); 7.17-7.39 (m, 5H, arom); 8.57 (s, 1H, NH); 8.39 (s, 2H, 2NH); 10.06 (s, 1H, NH). ¹³C NMR: 29.7, 47.0 (2x CH₂); 126.6, 139.1 (2x C₆H₄); 127.3, 127.4, 128.0 (5x C₆H₄); 139.4 (C=O); 182.7 (C=S). Anal. Calcd for C₁₁H₁₃N₇OS: C 45.35, H 4.50, N 33.65. Found: C 45.11, H 4.08, N 33.21.

3-[(Tetrazol-5-yl)methyl]-4-substituted-1,2,4-triazoline-5-thione (3a-3f)

General procedure
0.01 Mol of thiosemicarbazide (2a-2f) dissolved in 40-50 mL of 2% aqueous NaOH was refluxed for 2h. After cooling, the solution was neutralized with dilute hydrochloric acid. The precipitate was filtered off and crystallized from EtOH (62-80%). The results are collected in Table 2.

4-Phenyl-3-[(tetrazol-5-yl)methyl]-1,2,4-triazoline-5-thione (3a): mp 148-150 °C. IR (cm⁻¹): 3078 CH arom; 2976, 1440 CH aliph; 1710 C=O; 1563 C=N. ¹H NMR (DMSO-d₆) δ: 4.31 (s, 2H, CH₂); 6.89-7.58 (m, 5H, arom); 8.33 (s, 1H, NH); 13.98 (s, 1H, NH). Anal. Calcd for C₁₁H₁₁N₇S: C 48.34, H 4.06, N 35.87. Found: C 48.32, H 4.08, N 35.79.

4-(4-Tolyl)-3-[(tetrazol-5-yl)methyl]-1,2,4-triazoline-5-thione (3b): mp 153-155 °C. IR (cm⁻¹): 3060 CH arom; 2948, 1440 CH aliph; 1720 C=O; 1590 C=N; 1510 C-N. ¹H NMR (DMSO-d₆) δ: 2.35 (s, 3H, CH₃); 6.89-7.58 (m, 5H, arom); 8.33 (s, 1H, NH); 13.98 (s, 1H, NH). Anal. Calcd for C₁₂H₁₃N₇S: C 50.16, H 4.56, N 34.12. Found: C 50.13, H 4.54, N 34.10.

4-(4-Methoxyphenyl)-3-[(tetrazol-5-yl)methyl]-1,2,4-triazoline-5-thione (3c): mp 222-224 °C. IR (cm⁻¹):...
3065 CH arom; 2950, 1437 CH aliph; 1718 C=O; 1580 C=N; 1510 C-N. 1H NMR (DMSO-d6) δ: 3.79 (s, 3H, CH$_3$); 4.27 (s, 2H, CH$_2$); 6.80-7.40 (m, 4H, arom); 8.38 (s, 1H, NH); 13.88 (s, 1H, NH). Anal. Calcd for C$_{12}$H$_{13}$N$_7$S: C 47.51, H 4.32, N 32.32. Found: C 47.41, H 4.31, N 32.07.

4-(4-Bromophenyl)-3-[(tetrazol-5-yl)methyl]-1,2,4-triazoline-5-thione (3d): mp 256-258 ºC. IR (cm$^{-1}$): 3070 CH arom; 2953, 1432 CH aliph; 1718 C=O; 1578 C=N; 1510 C-N. 1H NMR (DMSO-d$_6$) δ: 4.34 (s, 2H, CH$_2$); 7.29-7.80 (m, 4H, arom); 8.59 (s, 1H, NH); 13.41 (s, 1H, NH). Anal. Calcd for C$_{11}$H$_{10}$BrN$_7$S: C 37.51, H 2.86, N 27.84. Found: C 37.26, H 2.80, N 27.72.

4-(2-Fluorophenyl)-3-[(tetrazol-5-yl)methyl]-1,2,4-triazoline-5-thione (3e): mp 177-179 ºC. IR (cm$^{-1}$): 3080 CH arom; 2957, 1433 CH aliph; 1720 C=O; 1570 C=N; 1509 C-N. 1H NMR (DMSO-d$_6$) δ: 4.32 (s, 2H, CH$_2$); 6.91-7.63 (m, 4H, arom); 8.38 (s, 1H, NH); 14.06 (s, 1H, NH). Anal. Calcd for C$_{11}$H$_{10}$FN$_7$S: C 45.35, H 3.46, N 33.66. Found: C 45.42, H 3.61, N 33.64.

4-Benzyl-3-[(tetrazol-5-yl)methyl]-1,2,4-triazoline-5-thione (3f): mp 163-165 ºC. IR (cm$^{-1}$): 3080 CH arom; 2952, 1428 CH aliph; 1718 C=O; 1580 C=N; 1505 C-N. 1H NMR (DMSO-d$_6$) δ: 4.38 (s, 2H, CH$_2$); 5.29 (s, 2H, CH$_2$); 7.11-7.37 (m, 5H, arom); 13.90 (s, 1H, NH); 16.05 (s, 1H, NH). 13C NMR: 21.1, 45.9 (2x CH$_2$); 126.8, 128.0, 128.9 (5x CH$_{ar}$), 135.1, 152.1 (2x CH$_{ar}$); 167.9 (C=S). Anal. Calcd for C$_{12}$H$_{13}$N$_7$S: C 50.16, H 4.56, N 34.12. Found: C 50.14, H 4.51, N 34.10.

Microbiology

Five compounds (2c, 2d, 2f, 3c, 3f) were screened for the in vitro antimicrobial activity using agar dilution method according to Clinical Laboratory Standards Institute (CLSI). In these studies 10 reference strains of aerobic bacteria (Staphylococcus aureus ATCC 25923, Staphylococcus epidermidis ATCC 12228, Bacillus subtilis ATCC 6633, Bacillus cereus ATCC 10876, Micrococcus luteus ATCC 10240, Escherichia coli ATCC 35218, Escherichia coli ATCC 25922, Proteus mirabilis ATCC 12453, Klebsiella pneumoniae ATCC 13883, Pseudomonas aeruginosa ATCC 9027) and 5 reference strains of fungi (Candida albicans ATCC 2091, Candida albicans ATCC 10231, Candida parapsilosis ATCC 22019, Trichophyton mentagrophytes ATCC 9533, Aspergillus niger ATCC 16404) were included. The inoculum density was adjusted to 0.5 McFarland standard with sterile saline (0.85% NaCl) and then the suspensions were diluted 1:10 in Mueller-Hinton broth (for bacteria) or Mueller-Hinton broth with 2% glucose (for fungi). All stock solutions of the assayed compounds were prepared in 100% dimethyl sulfoxide (DMSO).

In the agar dilution method, microbial suspensions were put onto Mueller-Hinton agar (for bacteria) or Mueller-Hinton agar with 2% glucose buffered at pH 5.6 (for fungi) containing several final concentrations of the tested compounds (31.25 - 500 mg L$^{-1}$). The plates were incubated at 37ºC for 18 h for bacteria and at 30ºC for 24 and 48 h for Candida spp. and for 72-96 h for Aspergillus niger ATCC.
16404 and *T. mentagrophytes* ATCC 9533, depending on the growth in control plates. It was found that DMSO at the final concentration in the medium had no influence on growth of the tested microorganisms. The MIC (Minimal Inhibitory Concentration) values were defined as the lowest concentration of the compound required to 100% inhibition of the visible growth of the tested bacteria or prominent growth inhibition (approximately 80% inhibition compared with the growth in the control plates) of fungi. The MICs were determined by comparison with the growth of control (compound–free) agar plates for bacteria or for fungi.

The antibacterial effect of the compound 2d on *M. luteus* ATCC 10240 growth was also determined by broth dilution method. After incubation (37°C for 18 h), optical density (OD 600) measurements were determined for bacterial culture in Mueller-Hinton broth containing from 0.12 to 500 mg L⁻¹ of the compound 2d. In our experiments, two cephalosporines - cefuroxime and cefazoline, were used as control agents in concentrations from 0.015 to 500 mg L⁻¹. All experiments were done three times and the representative values are presented.

Computational methods

Geometry optimization of tautomeric forms of 3c and 3f and compound 2d was carried out using at the density functional theory (DFT) level using the B3LYP functional¹⁹-²¹ and the standard 6-31+G(d,p) basis set²²-²³ as implemented in the Gaussian03 package.²⁴ All calculations were carried out using default convergence criteria. Vibrational analysis was performed for the optimized structures to confirm that they represent stationary points on the potential energy surfaces. Gas phase geometries were subsequently reoptimized using the same theory level and basis set, and the PCM implicit solvent model²⁵ with parameters corresponding to water and 1-octanol. Default parameters for water were used. Parameters used for 1-octanol are given in the Table 5.

Default UFF²⁶ radii of heavy atoms were used in the cavity building. Gibbs free energy values obtained in both solvents were used in calculations of logP values according to formula \((G_{aq} - G_{oct}) / 2.303RT\), where R is gas constant and T absolute temperature.

Table 5. Parameters used for 1-octanol

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<th>Property</th>
<th>Value</th>
</tr>
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<tr>
<td>Molar volume</td>
<td>158.474000 Å³</td>
</tr>
<tr>
<td>Numeral density</td>
<td>0.003826 Å⁻³</td>
</tr>
<tr>
<td>Thermal expansion coefficient</td>
<td>0.008270 K⁻¹</td>
</tr>
<tr>
<td>Solvent radius</td>
<td>0.4 Å</td>
</tr>
</tbody>
</table>

REFERENCES


