Synthesis, physical-chemical properties and the study of anti-hypoxemic activity of 5-(adamantane-1-yl)-4-R-1,2,4-triazole-3-thion alkyl derivatives

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Key words: Derivatives, 1,2,4-triazole, Physical-chemical Properties, Anti-hypoxemic Activity.

Objective. In order to identify the most promising active compounds, the pharmacological screening of anti-hypoxemic activity of synthesized compounds has been carried out.

Results. Due to the results of the study, a number of compounds with anti-hypoxemic activity have been revealed. Some regularities between structure and pharmacological effect have been established.

Conclusion. This demonstrates the prospects of further studies of the obtained compounds.

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Materials and methods of the study

The objects of study are alkyldervatives of 5-(adamantane-1-yl)-4-R-1,2,4-triazole-3-thions, where R is methyl, phenyl. As an initial matter, we have used 2-(adamantane-1-yl)-N-methylhydrazincarbothioamide or 2-(adamantane-1-yl)-N-phenylhydrazincarbothioamide and 2-(adamantane-1-yl)-N-methylhydrazincarbothioamide, which were synthesized by the reaction of hydrazide adamantane-1-carboxylic acid with phenylisothiocyanate and methylisothiocyanate, respectively, in the environment of methyl alcohol. Synthesis of 2-(adamantane-1-yl)-N-methylhydrazincarbothioamide or 2-(adamantane-1-yl)-N-phenylhydrazincarbothioamide and 2-(adamantane-1-yl)-N-methylhydrazincarbothioamide in an alkaline media. The obtaining of 3-alkythio-5-(adamantane-1-yl)-4-R-4H-1,2,4-triazole (comp. Ia-Ig, IIa-IIg) was carried out by adding α-haloalkanes to the corresponding 5-(adamantane-1-yl)-4-R-4H-1,2,4-triazole-3-thiones in the environment of n-butanol.

The obtained compounds are crystalline substances of white color, which were recrystallized from n-butanol for analysis. Physical-chemical constants of the obtained compounds are given in the table 1.

### Table 1

**Physical-chemical constants of 3-R1-thio-5-(adamantane-1-yl)-4-R-4H-1,2,4-triazole**

| № compounds | R  | R1 | T of melting. °C | gross formula | Output, % | Found, % | Calculated, % |
|-------------|----|----|------------------|---------------|----------|---------|--------------|
| I           | CH3| H  | 235-237          | C9H15NS       | 73.40    | C 62.61 | 68.55        |
| II          | C6H5| H  | 132-133          | C10H17NS      | 78.67    | C 62.45 | 71.82        |
| la          | CH3| H  | >230             | C9H16NS       | 73.77    | C 69.21 | 73.13        |
| lb          | CH3| H  | >230             | C9H16NS       | 74.50    | C 67.01 | 70.93        |
| lc          | CH3| H  | >230             | C9H16NS       | 80.52    | C 67.82 | 71.37        |
| ld          | CH3| H  | >230             | C9H16NS       | 75.54    | C 68.21 | 72.22        |
| le          | CH3| H  | 178-180          | C9H16NS       | 76.12    | C 69.30 | 73.16        |
| lf          | CH3| H  | >230             | C9H16NS       | 73.33    | C 69.54 | 73.27        |
| lg          | CH3| H  | >230             | C9H16NS       | 77.17    | C 70.17 | 74.17        |
| lla         | C6H5| H | >230             | C11H18NS      | 69.72    | C 70.72 | 74.82        |
| llb         | C6H5| H | 105-108          | C11H18NS      | 65.57    | C 72.06 | 76.19        |
| llc         | C6H5| H | >230             | C11H18NS      | 66.45    | C 72.25 | 76.65        |
| lld         | C6H5| H | >230             | C11H18NS      | 72.51    | C 73.05 | 77.38        |
| llc         | C6H5| H | 150-152          | C11H18NS      | 70.11    | C 73.08 | 77.19        |
| llf         | C6H5| H | >230             | C11H18NS      | 71.42    | C 73.93 | 78.02        |
| llg         | C6H5| H | >230             | C11H18NS      | 65.74    | C 73.91 | 78.34        |

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The research results are processed by modern statistical methods of analysis on a personal computer using standard software package Microsoft Office 2010 (Microsoft Excel) and «STATISTICA® for Windows 6.0». Average arithmetics (M) and standard errors of (± m) were calculated. Reliability of inter groups differences according to the experiments were established by using t-Student criterion. 3 levels of statistical significance of differences in the results of the research – p<0.05; p<0.01; and p<0.001 were used [10, 11].

The results and their discussion

The structure of all synthesized compounds has been confirmed by the integrated use of modern physical-chemical methods of analysis: elemental, IR spectroscopy and their individuality is detected by thin layer chromatography.

Band oscillations groups characteristic for the nucleus of 1,2,4-triazole: NH– within 3400–3100 cm⁻¹, –C=N– 1690–1620 cm⁻¹ are present in the IR spectra of compounds I, II. There are also present band oscillations groups –C–S in 705–570 cm⁻¹. There are band oscillations within 2600–2550 cm⁻¹, which may indicate to the presence of –S≤N group in the molecule.

The band oscillations groups characteristic for the nucleus of 1,2,4-triazole: NH– within 3400–3100 cm⁻¹, –C=N– 1690–1620 cm⁻¹ are available in the study of the IR spectra of Ia–Ig, IIa–IIG compounds. There are also present band oscillations groups –C–S in 705–570 cm⁻¹. There are band oscillations characteristic for a group –CH, within 2975–2950 cm⁻¹ and for a group –CH₂ – 2940–2915 cm⁻¹.

The signals of methyl group are present in the ¹H NMR spectra of 3-(adamantane-1-yl)-5-(butylthio)-4-phenyl-4H-1,2,4-triazole which are recorded in the spectrum in the form of a triplet multiplets at 0.89 m. h. (3H), 1.69 m. h. (3H) and deplete, 82 m. h. (6N), the signals of methine group at 1.28 (2N), 1.59 (2N), the signals of the protons of a methyl group, associated with sulphur within 2.93 m. h. (2N) and the protons of the aromatic cycle, which are fixed in the form of 2 triplets at 6.80 m. h. (1H), 7.18 m. h. (2N) and the multiplet of 7.48 m. h. (2N).

The most active was compound II, which is the derivative for the synthesis of the investigated alkylderivatives, its anti-hypoxemic activity exceeded the control on 169,10 % (p<0.001) and Mexidol on 30,90 % (p<0.001).

It is established that anti-hypoxemic activity in a series of alkylderivatives 5-(adamantane-1-yl)-4-R-1,2,4-triazole-3-thion (comp. I, II) due to the nature of the substituent at the N4 atom nitrogen of the nucleus of 1,2,4-triazole and the length of the

| № comp. | ¹H NMR spectra (DMSO-d6 δ ppm) |
|---------|----------------------------------|
| I       | 1,61 (t, 6H, CH₂), 1,73 (t, 3H, CH), 1,94 (d, 6H, CH₂), 3,61 (s, 3H, CH₃), 13,15 (s, 1H, SH) |
| II      | 1,59 (s, 6H, CH₂), 1,68 (t, 3H, CH), 1,85 (d, 6H, CH₂), 2,21 (t 1H, Ar-H), 7,52 (t 2H, Ar-H), 7,78 (t 2H, Ar-H), 13,15 (s, 1H, SH) |
| IIa     | 0,89 (t, 3H, CH₂), 1,28 (m, 2H, CH₂), 1,59 (m, 8H, CH₂), 1,69 (m, 3H, CH), 1,82 (m, 6H, CH₂), 2,93 (t 2H, CH₂), 6,80 (t 1H, Ar-H), 7,18 (t 2H, Ar-H), 7,48 (m, 2H, Ar-H) |
| Ib      | 1,60 (t, 3H, CH₂), 1,70 (m, 10H, CH₂), 1,92 (m, 2H, CH₂; 3Н, СН₂), 2,68 (d, 6H, CH₂), 3,12 (s, 3H, CH₃), 3,28 (t, 2H, CH₂) |
| Ic      | 0,82 (t, 3H, CH₂), 1,21 (m, 6H, CH₂), 1,60 (m, 8H, CH₂), 1,79 (m, 3H, CH), 2,00 (d, 6H, CH₂), 3,35 (s, 3H, CH₃), 3,62 (t, 3H, CH₂) |
| If      | 0,82 (t, 3H, CH₂), 1,22 (m, 12H, CH₂), 1,60 (m, 8H, CH₂), 1,79 (m, 3H, CH), 2,00 (d, 6H, CH₂), 3,35 (s, 3H, CH₃), 3,62 (t, 3H, CH₂) |
| Ig      | 0,82 (t, 3H, CH₂), 1,22 (m, 14H, CH₂), 1,60 (m, 8H, CH₂), 1,79 (m, 3H, CH), 2,00 (d, 6H, CH₂), 3,35 (s, 3H, CH₃), 3,62 (t, 3H, CH₂) |

Table 2

The characteristic of ¹H NMR spectra of the obtained compounds

Table 3

Anti-hypoxemic activity of alkylderivatives 5-(adamantane-1-yl)-4-R-1,2,4-triazole-3-thion (n=7)

| Compound / group | Dose compounds, mg/kg | The average life span of rats min. | Activity accordingly to contro l% | Activity accordingly to Mexidol, Δ% |
|------------------|----------------------|----------------------------------|----------------------------------|-----------------------------------|
| control          | -                    | 66,57±1,86                       | -                                | -22,59                            |
| Mexidol          | 100                  | 86,00±2,26                       | 129,18                           | -                                 |
| I                | 84,2                 | 73,71±2,71                       | 110,73                           | -14,29                            |
| II               | 357                  | 112,57±3,69*                     | 169,10                           | 30,90                             |
| IIa              | 56,5                 | 80,43±6,17**                     | 120,82                           | -6,48                             |
| control          | -                    | 54,29±4,45                       | -                                | -30,15                            |
| Mexidol          | 100                  | 77,71±9,4*                       | 143,16                           | -                                 |
| Ib               | 62,4                 | 78,00±5,18*                      | 143,68                           | 0,37                              |
| Ic               | 125                  | 82,43±5,55*                      | 151,84                           | 6,07                              |
| If               | 182                  | 56,57±4,43                       | 104,21                           | -27,21                            |
| Ig               | 153                  | 61,43±5,98                       | 113,16                           | -30,86                            |
| IIb              | 132                  | 75,29±4,98*                      | 138,68                           | -3,12                             |
| IId              | 166                  | 100,14±4,95*                     | 184,47                           | 28,86                             |
| Ile              | 174                  | 55,88±6,99                       | 102,93                           | -28,10                            |
| IIg              | 179                  | 98,14±13,64*                     | 180,79                           | 26,29                             |

Notes: * – p<0.05 relatively to control; ** – p<0.05 relatively to Mexidol; n – the number of animals in each group of the research.

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carbon chain alkyl residue with the sulfur atom.

The compounds Ic and Iig showed antihypoxic activity, which exceeds the control on 184.47% (p<0.01) and 180.79% (p<0.05) and were higher than the activity of the Mexidol on 28.86 and 26.29%, respectively.

Ib and Ic compounds are close to Mexidol activity, but well worth to note the Ibb compound, which 3.12% less efficient than Mexidol.

The analysis of the results indicates high antihypoxic activity due to the life expectancy indicator of rats of all studied substances in comparison with the control.

As a result of the studies (II, IIC, IIg) compounds were identified, which antihypoxic activity higher than Mexidol the comparison product.

Analyzing the dependence of the chemical structure from antihypoxic activity certain patterns were established between pharmacological activity and chemical structure. Thus, the antihypoxic activity of the transition from alicyclic to hexilene substituents in the molecules of 3-alkythio-5-(adamantane-1-yl)-4-methyl(phenyl)-1,2,4-triazole, the degree of which depends on the substituent at the N4 atom of nitrogen (Ib, Ic, Iib, Ilc comp.).

A significant reduction of antihypoxic activity is observed with increasing carbon chain to heptile, octilene and nonilene substituents in the case, as with methyl and phenyl substituents (Ile, Iid, If). But the growth up to ten carbon atoms promotes the growth of antihypoxic activity (comp. Iig).

Conclusions

1. A number of new compounds, derivatives of 5-(adamantane-1-yl)-4-R-1,2,4-triazole-3-thiones, have been synthesized. The structure of these compounds has been confirmed by the integrated use of modern physical-chemical methods of analysis.

2. The most active among the investigated compounds are 5-(adamantane-1-yl)-4-phenyl-1,2,4-triazole-3-thion, its antihypoxic activity exceeds the control on 169.10% (p<0.001) and Mexidol on 30.90% (p<0.001).

3. Iig IIC compounds exceed the activity of Mexidol on 28.86% (p<0.01) and on 26.29% (p<0.01), respectively.

4. The significant intensification of antihypoxic activity in the transition from alicyclic to hexilene substituents in the molecules of 3-alkythio-5-(adamantane-1-yl)-4-methyl(phenyl)-1,2,4-triazole, the degree of which depends on the substituent at the N4 atom of nitrogen.

5. It was established that the methyl radical replacing on phenyl substituent at N4 atom of nitrogen enhances antihypoxic activity.

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