Synthesis and properties of S-derivatives of 4-amino-5-(5-methylpyrazol-3-yl)-1,2,4-triazole-3-thiol

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

The combination of various heterocyclic systems with a wide range of properties is quite expedient and is, in practice, a justified direction for obtaining biologically active substances, which ultimately forms a favorable basis for the creation of drugs. In recent decades, the attention of scientists has been closely focused on nitrogen-containing heterocyclic compounds.

Among such compounds, 1,2,4-triazole and pyrazole occupy a special place. Indeed, on the basis of these systems, a significant number of well-known drugs have been created, which are widely used at the present time.

The aim of the work was the synthesis of S-derivatives of 4-amino-5-(5-methylpyrazol-3-yl)-1,2,4-triazole-3-thiol, study of their physical and chemical properties, pre-screening studies with subsequent establishment of the feasibility of further pharmacological studies.

Materials and methods. Experimental methods of organic chemistry: synthesis using microwave activation, physical and chemical methods for the analysis of organic compounds (determination of the melting point, elemental analysis, 1H NMR, IR spectroscopy and chromatography-mass spectrometry). Methods for in silico pre-screening studies to establish the biological potential in several synthesized compounds (molecular docking).

Results. 10 new S-derivatives of 4-amino-5-(5-methylpyrazol-3-yl)-1,2,4-triazole-3-thiol were synthesized. The structure of the obtained compounds was confirmed by a set of physical and chemical methods of analysis. According to the results of prescreening studies, the main directions of research of biological properties of synthesized compounds were provided.

Conclusions. The expediency of using microwave irradiation in the synthesis of a series of S-alkyl derivatives of 4-amino-5-(5-methylpyrazol-3-yl)-1,2,4-triazole-3-thiol had been proved. Based on the results of in silico studies, the expediency of further studies of anti-inflammatory, antifungal and anticancer activities in several synthesized compounds had been substantiated.

Key words: 5-methylpyrazole, 1,2,4-triazole, synthesis, properties, molecular docking.

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Синтез и свойства S-производных 4-амино-5-(5-метилпиразол-3-ил)-1,2,4-триазол-3-тиола
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Целесообразно сочетание различных гетероциклических систем с широким набором свойств, так как это оправданное на практике направление получения биологически активных субстанций. В итоге это формирует основу для создания лекарственных средств. В последние десятилетия внимание учёных приковано к азотсодержащим гетероциклическим соединениям. Особое место среди них занимают 1,2,4-триазол и пиразол, ведь на основе этих систем было создано значительное количество известных лекарственных средств, которые достаточно широко используют.

Цель работы — синтез S-производных 4-амино-5-(5-метилпиразол-3-ил)-1,2,4-триазол-3-тиола, изучение их физико-химических свойств, проведение прескрининговых исследований с установлением целесообразности дальнейших фармакологических исследований.

Материалы и методы. Применили экспериментальные методы органической химии: синтез с использованием микроволновой активации, физико-химические методы анализа органических соединений (определение температуры плавления, элементный анализ, 'Н ЯМР, ИК-спектроскопия и хромато-масс-спектрометрия). Провели прескрининговые исследования in vitro для установления целесообразности потенциала в ряду синтезированных соединений (мoleкулярный докинг).

Результаты. Установлены оптимальные условия получения 10 новых S-производных 4-амино-5-(5-метилпиразол-3-ил)-1,2,4-триазол-3-тиола с использованием микроволнового облучения. Строение полученных соединений подтверждено комплексом физико-химических методов анализа. По результатам прескринингового анализа определены основные направления исследований биологических свойств синтезированных соединений.

Выводы. Доказана целесообразность применения микроволнового облучения при синтезе ряда S-алкилированных 4-амино-5-(5-метилпиразол-3-ил)-1,2,4-триазол-3-тиола. По результатам исследования in vitro обоснована целесообразность дальнейшего изучения противовоспалительной, противогрибковой и противораковой активностей в ряду синтезированных соединений.

Ключевые слова: 5-метилпиразол, 1,2,4-триазол, синтез, свойства, молекулярный докинг.

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Results

Analysis of $^1$H NMR spectra showed that the protons of S-alkyl fragments resonate in a strong part of the field in the form of signals with different intensities in the range 3.14–0.82 ppm. For example, singlet signals of methyl protons of the thiomethyl fragment were present in the range of 3.14–3.08 ppm. Multiple proton signals of methylene fragments were recorded in a stronger field (1.97–1.20 ppm). A gradual increase in the length of the S-alkyl chain leads to a slight shift in the signals of the protons of the methyl group in the stronger part of the field.

Proton signals of methylene moieties of S-alkyl substituents were conducted in a similar way but were difficult to differentiate because they form mostly multiproton multiplets. Exceptions were only signals of protons of the methylene group directly with the sulfur atom. In this case, there was a signal in the form of a triplet. The formation of a positive inductive effect contributed to these changes. Thus, the signal of protons of the methyl group gradually shifts to 0.83 ppm.

The IR spectrum of the synthesized thiol (2.0) was characterized by the presence of clear bands of deformation and valence oscillations of strong and medium intensity of the main fragments of the molecule: planar deformation oscillations CH in the region 1229–1182 cm\(^{-1}\) (bands of low intensity at 1229–1182 cm\(^{-1}\), 1045–1029 cm\(^{-1}\), 1013–998 cm\(^{-1}\), 975–960 cm\(^{-1}\)), out-of-plane deformation oscillations CH in the region 998–663 cm\(^{-1}\) (bands of strong intensity at 781–765 cm\(^{-1}\), 687–672 cm\(^{-1}\)). There was the presence of a band of valence vibrations of the SH group in the range of 2928–2380 cm\(^{-1}\). The oscillation bands of the C=N fragment in the region of 1548–1530 cm\(^{-1}\) were also recorded.

In the spectra of the synthesized alkyl derivatives (2.0–2.10) deformation oscillations of alkyl groups in the range from 645 cm\(^{-1}\) to 1390 cm\(^{-1}\) and the H-C-H fragment in the narrow frequency range 1485–1360 cm\(^{-1}\) were observed. In the spectra of the synthesized alkyl derivatives (2.1–2.10) deformation oscillations of alkyl groups in the range from 645 cm\(^{-1}\) to 1390 cm\(^{-1}\) and the H-C-H fragment in the narrow frequency range 1485–1360 cm\(^{-1}\) were observed.

4-Amino-5-(5-methylpyrazol-3-yl)-1,2,4-triazole-3-thiol (2.0).

Yield: 71 %; m. p.: 218–216 °C; $^1$H NMR, d, ppm: 13.74 (s, 1H, SH); 13.11 (1H, s, NH-pyrazole), 6.63 (s, 1H, CH-pyrazole), 5.98 (s, 2H, NH$_2$), 2.26 (s, 3H, CH$_3$-pyrazole). ESI-MS: m/z = 197 [M+H]$^+$. Analytical calculated (%) for C$_{16}$H$_{16}$N$_4$S: C, 36.72; H, 4.11; N, 42.83; S, 16.34. Found: C, 36.81; H, 4.12; N, 42.75; S, 16.32.

3-(5-Methylpyrazol-3-yl)-5-methylthio-1,2,4-triazole-4-amine (2.1).

Yield: 79 %; m. p.: 193–191 °C; $^1$H NMR, d, ppm: 13.07 (s, 1H, NH-pyrazole), 6.65 (s, 1H, CH-pyrazole), 6.02 (s, 2H, NH$_2$), 2.67 (t, 3H, S-CH$_3$), 2.33 (s, 3H, CH$_3$-pyrazole). ESI-MS: m/z = 211 [M+H]$^+$. Analytical calculated (%) for C$_{16}$H$_{19}$N$_4$S: C, 39.99; H, 4.79; N, 39.97; S, 15.02. Found: C, 39.89; H, 4.80; N, 39.87; S, 15.29.

3-Ethylthio-5-(5-methylpyrazol-3-yl)-1,2,4-triazole-4-amine (2.2).

Yield: 82 %; m. p.: 193–194 °C; $^1$H NMR, d, ppm: 13.10 (s, 1H, NH-pyrazole), 6.61 (s, 1H, CH-pyrazole), 6.05 (s, 2H, NH$_2$), 3.13 (t, 2H, S-CH$_2$-CH$_2$), 2.30 (s, 3H, CH$_3$-pyrazole), 1.36 (t, 3H, S-CH$_2$-CH$_2$). ESI-MS: m/z = 225 [M+H]$^+$. Analytical calculated (%) for C$_{16}$H$_{16}$N$_4$S: C, 39.84; H, 5.39; N, 37.47; S, 14.29. Found: C, 39.74; H, 5.38; N, 37.56; S, 14.32.

3-(5-Methylpyrazol-3-yl)-5-propylthio-1,2,4-triazole-4-amine (2.3).

Yield: 76 %; m. p.: 186–184 °C; $^1$H NMR, d, ppm: 13.05 (s, 1H, NH-pyrazole), 6.67 (s, 1H, CH-pyrazole), 6.01 (s, 2H, NH$_2$), 3.11 (t, 2H, S-CH$_2$-CH$_2$), 2.35 (s, 3H, CH$_3$-pyrazole), 1.92–1.56 (m, 2H, S-CH$_2$-CH$_2$-CH$_2$), 1.05 (s, 3H, S-(CH$_3$)$_2$-CH$=$). ESI-MS: m/z = 239 [M+H]$^+$. Analytical calculated (%) for C$_{16}$H$_{21}$N$_4$S: C, 45.36; H, 5.92; N, 35.27; S, 13.45. Found: C, 45.47; H, 5.91; N, 35.18; S, 13.41.

3-Butylthio-5-(5-methylpyrazol-3-yl)-1,2,4-triazole-4-amine (2.4).

Yield: 71 %; m. p.: 182–180 °C; $^1$H NMR, d, ppm: 13.08 (s, 1H, NH-pyrazole), 6.63 (s, 1H, CH-pyrazole), 6.04 (s, 2H, NH$_2$), 3.14 (t, 2H, S-CH$_2$-(CH$_2$)$_2$-CH$_3$), 2.30 (s, 3H, CH$_3$-pyrazole), 1.84–1.50 (m, 2H, S-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 1.46–1.33 (m, 2H, S-(CH$_3$)$_2$-CH$=$-CH$_2$), 0.92 (t, 3H, S-(CH$_3$)$_2$-CH$=$). ESI-MS: m/z = 253 [M+H]$^+$. Analytical calculated (%) for C$_{16}$H$_{23}$N$_4$S: C, 47.60; H, 6.39; N, 33.31; S, 12.71. Found: C, 47.49; H, 6.40; N, 33.23; S, 12.74.

3-(5-Methylpyrazol-3-yl)-5-pentylthio-1,2,4-triazole-4-amine (2.5).

Yield: 74 %; m. p.: 172–174 °C; $^1$H NMR, d, ppm: 13.04 (s, 1H, NH-pyrazole), 6.57 (s, 1H, CH-pyrazole), 6.07 (s, 2H, NH$_2$), 3.10 (t, 2H, S-CH$_2$-(CH$_2$)$_3$-CH$_3$), 2.33 (s, 3H, CH$_3$-pyrazole), 1.87 – 1.55 (m, 2H, (m, 2H, S-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH$_3$), 1.49 1.25 (m, 4H, S-(CH$_2$)$_2$-(CH$_2$)$_2$-CH$_3$), 0.83
3-Heptylthio-5-(5-methylpyrazol-3-yl)-1,2,4-triazole-4-amine
Yield: 70%; m. p.: 170–172 °C; 1H NMR, d, ppm: 13.09 (s, 1H, NH-pyrazole), 6.07 (s, 2H, NH2), 3.08 (t, 2H, S-CH2-(CH2)2-CH2), 2.32 (s, 3H, CH3-pyrazole), 1.74–1.63 (m, 2H, S-CH2-(CH2)2-CH2), 1.31–1.22 (m, 8H, S-(CH2)2-CH2), 0.82 (t, 3H, S-(CH3)2-C2H5).

3-Heptylthio-5-(5-methylpyrazol-3-yl)-1,2,4-triazole-4-amine (2.7). Yield: 70%; m. p.: 170–172 °C; 1H NMR, d, ppm: 13.09 (s, 1H, NH-pyrazole), 6.07 (s, 2H, NH2), 3.08 (t, 2H, S-CH2-(CH2)2-CH2), 2.32 (s, 3H, CH3-pyrazole), 1.74–1.63 (m, 2H, S-CH2-(CH2)2-CH2), 1.31–1.22 (m, 8H, S-(CH2)2-CH2), 0.82 (t, 3H, S-(CH3)2-C2H5).

3-Hexylthio-5-(5-methylpyrazol-3-yl)-1,2,4-triazole-4-amine
Yield: 74%; m. p.: 162–164 °C; 1H NMR, d, ppm: 13.06 (s, 1H, NH-pyrazole), 6.06 (s, 2H, NH2), 3.10 (t, 2H, S-CH2-(CH2)2-CH2), 2.33 (s, 3H, CH3-pyrazole), 1.82–1.56 (m, 2H, S-CH2-(CH2)2-CH2), 1.43–1.22 (m, 10H, S-(CH2)2-CH2), 0.86 (t, 3H, S-(CH3)2-C2H5).

3-(5-Methylpyrazol-3-yl)-5-octylthio-1,2,4-triazole-4-amine
Yield: 74%; m. p.: 162–164 °C; 1H NMR, d, ppm: 13.10 (s, 1H, NH-pyrazole), 6.07 (s, 2H, NH2), 3.10 (t, 2H, S-CH2-(CH2)2-CH2), 2.34 (s, 3H, CH3-pyrazole), 1.69–1.51 (m, 2H, S-CH2-(CH2)2-CH2), 1.39–1.24 (m, 6H, S-(CH2)2-(CH2)2-CH2), 0.84 (t, 3H, S-(CH3)2-C2H5).

3-(5-Methylpyrazol-3-yl)-5-nonylthio-1,2,4-triazole-4-amine
Yield: 70%; m. p.: 166–168 °C; 1H NMR, d, ppm: 13.11 (s, 1H, NH-pyrazole), 6.55 (s, 1H, CH-pyrazole), 6.07 (s, 2H, NH2), 3.08 (t, 2H, S-CH2-(CH2)2-CH2), 2.32 (s, 3H, CH3-pyrazole), 1.74–1.63 (m, 2H, S-CH2-(CH2)2-CH2), 1.31–1.22 (m, 8H, S-(CH2)2-CH2), 0.82 (t, 3H, S-(CH3)2-C2H5).

H NMR, d, ppm: 13.06 (s, 1H, NH-pyrazole), 6.07 (s, 2H, NH2), 3.08 (t, 2H, S-CH2-(CH2)2-CH2), 2.34 (s, 3H, CH3-pyrazole), 1.69–1.51 (m, 2H, S-CH2-(CH2)2-CH2), 1.39–1.24 (m, 6H, S-(CH2)2-(CH2)2-CH2), 0.84 (t, 3H, S-(CH3)2-C2H5).

ESI-MS: m/z = 309 [M+H]+. Analytical calculated (%) for C19H24N8S: C, 54.52; H, 7.84; N, 27.25; S, 10.41.

ESI-MS: m/z = 295 [M+H]+. Analytical calculated (%) for C19H24N8S: C, 53.12; H, 7.53; N, 28.54; S, 10.89.

ESI-MS: m/z = 281 [M+H]+. Analytical calculated (%) for C19H24N8S: C, 51.30; H, 7.18; N, 29.91; S, 11.45.

Chromato-mass spectrum of compound 2.0.

Chromato-mass spectrum of compound 2.2.

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Table 1. Energy values of the intermolecular interactions of the studied compounds with COX-1 (3N8Y)

| N  | $E_{\text{min}}$ kcal/mol | N  | $E_{\text{min}}$ kcal/mol | N  | $E_{\text{min}}$ kcal/mol |
|----|---------------------------|----|---------------------------|----|---------------------------|
| 2.0 | -4.9                      | 2.4 | -5.7                      | 2.8 | -7.0                      |
| 2.1 | -4.5                      | 2.5 | -6.1                      | 2.9 | -7.3                      |
| 2.2 | -5.0                      | 2.6 | -5.5                      | 2.10 | -7.0                      |
| 2.3 | -5.3                      | 2.7 | -6.6                      | Diclofenac | -6.2 |

$E_{\text{min}}$: the minimum energy of complex formation.

Table 2. Energy values of the intermolecular interactions of the studied compounds with lanosterol-14α-demethylase (3LD6)

| N  | $E_{\text{min}}$ kcal/mol | N  | $E_{\text{min}}$ kcal/mol | N  | $E_{\text{min}}$ kcal/mol |
|----|---------------------------|----|---------------------------|----|---------------------------|
| 2.0 | -4.9                      | 2.4 | -7.5                      | 2.8 | -8.4                      |
| 2.1 | -6.5                      | 2.5 | -7.7                      | 2.9 | -8.9                      |
| 2.2 | -6.6                      | 2.6 | -8.1                      | 2.10 | -9.4                      |
| 2.3 | -6.8                      | 2.7 | -8.1                      | Ketoconazole | -8.1 |

$E_{\text{min}}$: the minimum energy of complex formation.

ESI-MS: $m/z = 323$ [M+H]$^+$. Analytical calculated (%) for C$_{13}$H$_{15}$N$_{5}$S: C, 55.87; H, 8.13; N, 26.06; S, 9.94. Found: C, 55.76; H, 8.12; N, 26.11; S, 9.96.

3-Decyldithio-5-(5-methylpyrazol-3-yl)-1,2,4-triazole-4-amine (2.10). Yield: 68%; m. p.: 158–160 °C; $^1$H NMR, $d$, ppm: 13.11 (s, 1H, NH-pyrazole), 6.53 (s, 1H, CH-pyrazole), 6.05 (s, 2H, NH$_2$), 3.10 (t, 2H, S-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$), 2.33 (s, 3H, CH$_3$-pyrazole), 1.74–1.63 (m, 2H, S-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$), 1.41–1.30 (m, 2H, S-(CH$_2$)$_2$-CH$_2$-CH$_2$-CH$_2$), 1.34–1.20 (m, 12H, S-(CH$_2$)$_2$-(CH$_2$)$_2$-CH$_2$), 0.82 (t, 3H, S-(CH$_2$)$_2$-CH$_2$). ESI-MS: $m/z = 337$ [M+H]$^+$. Analytical calculated (%) for C$_{13}$H$_{15}$N$_{5}$S: C, 57.11; H, 8.39; N, 26.11; S, 9.53. Found: C, 57.21; H, 8.40; N, 26.93; S, 9.50.

Individual peaks of molecular ions [M+1] were recorded in the chromat-mass spectra, which had a high intensity, which confirms the structure and individuality of the compounds (Fig 2, 3).

Molecular docking. It is noteworthy that a significant number of antifungal drugs contain a fragment of 1,2,4-triazole (fluconazole, itraconazole, voriconazole, posaconazole). Triazole-containing anastrozole and letrozole were also quite effective anticancer agents. On the other hand, the presence of pyrazole enzyme indicates the feasibility of testing for effective anticancer drugs. On the other hand, the presence of antifungal compounds that synthesized compounds form chemical bonds with the following amino acid residues: ASN B: 68, TYR B: 38, TYR B: 39. At the same time, the presence of π-alkyl hydrophobic interactions with such amino acid residues as LYS B: 4668, PRO B: 35, PRO B: 40, PRO B: 434, TYR B: 38, TYR B: 55.

Visualization of the interaction of active structures with the active site of lanosterol-14α-demethylase revealed that they have chemical bonds with the following amino acid residues: GLY A: 310, HIS A: 381, ILE A: 139, LEU A: 380, MET A: 509, PHE A: 134, PHE A: 241, PHE A: 384, TYR A: 126, VAL A: 311 (Fig 4). The estimated free energy of binding of the synthesized substances of their lowest energy positions with lanosterol-14α-demethylase was calculated (Table 2). Synthesized substances 2.6–2.10 showed a good range of binding energies from -8.1 to -9.4 kcal/mol.

The obtained substances were stabilized in the active center of anaplastic lymphoma kinase due to intermolecular hydrogen chemical bond with MET A: 1199, alkyl hydrophobic...
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with ALA A: 1200, LEU A: 1122, LEU A: 1196, LEU A: 1198, LEU A: 1256, LYS A: 1150 (Fig. 5). Moreover, attention is drawn to the presence of a certain amount of π-alkyl and π-anion hydrophobic interactions with the active site of the enzyme (with ALA A: 1200, LEU A: 1122 and GLU A: 1122), which had an immediate effect on the stability of a particular biologically active substance in the active site (Fig. 5).

Calculations of the free binding energy showed that an increase in the length of the S-alkyl fragment of the synthesized substances can have a positive effect on the affinity with the active site of the enzyme (Table 3). The most significant level of interaction with the active center of the enzyme were demonstrated by substances 2.8 and 2.10 with values of the free energy of interaction -8.0 kcal/mol and -8.4 kcal/mol accordingly (Table 3).

Discussion

The performed docking studies suggest that the synthesized S-alkyl derivatives exhibit the ability to bind to the active sites of COX-1, lanosterol 14-α-demethylase, and anaplastic lymphoma kinase.

It is also necessary to emphasize the participation of all fragments of molecules of new substances in interactions with the active site of enzymes.

**Table 3. Energy values of the intermolecular interactions of the studied compounds with anaplastic lymphoma kinase (2XP2)**

| N  | $E_{\text{min}}$ kcal/mol | N  | $E_{\text{max}}$ kcal/mol | N  | $E_{\text{min}}$ kcal/mol |
|----|--------------------------|----|---------------------------|----|--------------------------|
| 2.0| -5.5                     | 2.4| -6.7                      | 2.8| -8.0                     |
| 2.1| -5.2                     | 2.5| -6.5                      | 2.9| -7.9                     |
| 2.2| -6.0                     | 2.6| -6.8                      | 2.10| -8.4                      |
| 2.3| -6.4                     | 2.7| -7.4                      | Crizotinib| -7.6 |

$E_{\text{min}}$: the minimum energy of complex formation.
Comparison of the calculated $E_{\text{conf}}$ values in the series of synthesized substances made it possible to establish the effect of the length of the S-alkyl fragment on the affinity with the active site of the enzymes under consideration. Moreover, the transition from a methyl substituent to a decyl substituent was accompanied by an increase in this affinity. Alkyl hydrophobic interactions of the synthesized substances with amino acid residues of the corresponding enzymes had a significant influence on the formation of this dependence.

Conclusions

1. Using the appropriate bromalones as alkylating agents (bromopropane, bromobutane, bromopentane, bromhexane, bromoheptane, bromoctane, bromonan, bromodecane), the reaction of nucleophilic substitution 4-amino-5-(5-methylpyrazol-3-yl)-1,2,4-triazole-3-thiol was investigated. 10 new compounds were obtained. The structure was confirmed by complex modern physical and chemical methods of analysis (elemental analysis, PMR spectroscopy, chromatographic mass spectrometry), and their individuality was chromatographic.

2. The performed docking studies suggest that an increase in the length of the S-alkyl fragment increases the likelihood of anti-inflammatory, antifungal, and antitumor activity. Moreover, in molecules with an even number of carbon atoms in the alkyl substituent, this probability will only increase.

Prospects for further research. According to the research results it is planned to expand the line of this class of compounds to identify promising biologically active compounds among them.

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Conflicts of interest: authors have no conflict of interest to declare.

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