Some transformations in a series of 4-amino-1,2,4-triazole-3-thion derivatives

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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 continuous improvement of synthesis methods enables the optimization of the process for developing and obtaining target products of chemical transformation. Derivatives of 1,2,4-triazole-3-thiol present a convenient object for chemical transformation, facilitating the creation of promising biologically active compounds. Combining the structure of this heterocyclic system with pharmacophore fragments of different natures allows for more effective work on the development of molecules with high pharmacological potential. To implement this strategy, 2-,3-,4-fluorophenyl-4-amino-1,2,4-triazol-3-thiones were utilized as starting structures. This molecule possesses three reaction centers, facilitating a wide range of chemical transformations involving these substances.

The aim of the work was to create a series of 4-amino-2-((R_1,R_2-amino)methyl)-5-((2-,3-,4)-fluorophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones as a promising source for the preparation of biologically active substances.

Materials and methods. The structure of the target compounds has been formed using well-known methods of organic chemistry. The starting materials used were 2-,3-,4-fluorophenyl-4-amino-1,2,4-triazol-3-thiones, which were previously obtained. The first stage of the work involved the temporary protection of the amino group with a *tert*-butoxycarbonyl group. The second stage of the work involved the realization of Mannich reactions involving primary and secondary amines. The reaction has been carried out with formalin in an alcohol-dioxane medium. The products of the chemical transformation have been recrystallized in methanol. The third stage of the work was based on the removal of *Boc*-protection, which was realized using hydrochloric acid in a dioxane medium. The structures of all synthesized substances have been determined by ^{1}H NMR spectroscopy and elemental analysis. The individuality of the compounds has been confirmed by high-performance liquid chromatography.

Results. The successful study of the mechanisms of Mannich reactions for 4-amino-1,2,4-triazole-3-thione derivatives allowed us to obtain 4-amino-2-((R_1,R_2-amino)methyl)-5-((2-,3-,4)-fluorophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones in quantitative yields. The studies made it possible to establish the favorable effect of protecting the amino group of the 2-,3-,4-fluorophenyl-4-amino-1,2,4-triazole-3-thione of the *tert*-butyloxycarbonyl group on the course and direction of the reaction.

Conclusions. The optimal conditions for the Mannich reactions involving 2-,3-,4-fluorophenyl-4-amino-1,2,4-triazole-3-thione with intermediate Boc-protection of the amino group have been determined, which allowed us to create the theoretical basis for the successful use of Mannich reactions to expand the range of promising 4-amino-1,2,4-triazole-3-thione derivatives.

Keywords: Mannich bases, physicochemical properties, spectral characteristics.

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Деякі перетворення в ряду похідних 4-аміно-1,2,4-тріазол-3-тіону

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Постійне вдосконалення методів синтезу дає змогу оптимізувати процес розробки й одержання цільових продуктів хімічного перетворення. Похідні 1,2,4-тріазол-3-тіолу є зручним об'єктом для хімічної трансформації, і тому за їх участю можна створювати перспективні біологічно активні сполуки. Поєднання структури зазначеної гетероциклічної системи з фармакофорними фрагментами іншої природи забезпечує ефективнішу роботу в напрямі розроблення молекул із високим фармакологічним потенціалом. Для реалізації цієї стратегії як вихідні структури використали 2-,3-,4-фторофеніл-4-аміно-1,2,4-тріазол-3-тіони. Ця молекула характеризується наявністю трьох реакційних центрів, що сприяє реалізації широкого спектра хімічних перетворень за участю зазначених речовин.

Мета роботи – створення ряду 4-аміно-2-((R_1,R_2-аміно)метил)-5-((2-,3-,4)-фторофеніл)-2,4-дигідро-3*H*-1,2,4-тріазол-3-тіонів як перспективного джерела для одержання біологічно активних речовин.

Матеріали і методи. Структуру цільових сполук сформували, застосувавши відомі методи органічної хімії. Як вихідні речовини використали попередньо одержані 2-,3-,4-фторофеніл-4-аміно-1,2,4-тріазол-3-тіони. Перший етап роботи передбачав тимчасовий

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захист аміногрупи *трет*-бутоксикарбонільною групою. Другий етап роботи – реалізація реакцій Манніха за участю первинних і вторинних амінів. Реакцію проводили із залученням формаліну у спиртово-діоксановому середовищі. Продукти хімічного перетворення перекристалізовано в середовищі метанолу. На третьому етапі роботи знято *Boc*-захист; це реалізовано з застосуванням кислоти хлоридної в середовищі діоксану. Структуру всіх синтезованих речовин визначено за допомогою ^{1}H ЯМР-спектроскопії та елементного аналізу. Індивідуальність сполук підтверджена методом високоефективної рідинної хроматографії.

Результати. Успішне дослідження механізмів перебігу реакцій Манніха для похідних 4-аміно-1,2,4-тріазол-3-тіону дало змогу з кількісними виходами одержати 4-аміно-2-((R_1,R_2-аміно)метил)-5-((2-,3-,4)-фторофеніл)-2,4-дигідро-3*H*-1,2,4-тріазол-3-тіони. У результаті дослідження встановили сприятливий вплив захисту аміно-групи 2-,3-,4-фторофеніл-4-аміно-1,2,4-тріазол-3-тіону *трет*-бутилоксикарбонільної групи на перебіг і напрям реакції.

Висновки. Визначили оптимальні умови проведення реакцій Манніха за участю 2-,3-,4-фторофеніл-4-аміно-1,2,4-тріазол-3-тіону з проміжним *Boc*-захистом аміногрупи. Це дало змогу створити теоретичні засади успішного використання реакцій Манніха для розширення спектра перспективних похідних 4-аміно-1,2,4-тріазол-3-тіону. Щодо синтезованих сполук надалі заплановано вивчення біологічної активності методами комп'ютерного прогнозування та *in vivo* дослідження аналгетичної, нейропротективної активності, противірусної та антимікробної дії.

Ключові слова: основи Манніха, фізико-хімічні властивості, спектральні характеристики.

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To expand the arsenal of new biologically active molecules, there is a constant need for targeted research in several synthetic compounds. This, in turn, contributes to solving the urgent problem of creating new highly effective and low-toxic drugs, the demand for which is growing dynamically in the modern world. The creation of new, original molecules of synthetic origin, which in a short time can turn into effective biologically active compounds, and later into modern effective drugs, is, in our opinion, an urgent task [1,2].

Analyzing scientific achievements, our attention was drawn to nitrogen-containing heterocyclic systems [3,4,5]. Separate attention should be paid to 1,2,4-triazole derivatives, which will attract scientists of various scientific fields for a long time [6,7,8,9]. Today, it can be confidently stated that the modern trend is the possibility of combining 1,2,4-triazole with various pharmacophoric substituents, which are oriented according to different positions. Amines are very important representatives of organic compounds, as well as functional groups of various substances. They actively participate in the formation of hydrogen bonds, can be both acceptors and donors of hydrogen bonds. In many cases, amines exhibit a strong ionic interaction with the electron-negative part in the binding site, so, for example, tertiary aliphatic amine is one of the most popular functional groups in pharmaceuticals.

Thus, despite the importance of amines, current methods for their synthesis are still limited. The development of a mild, modular and efficient synthesis of amine derivatives is still a need in medicinal chemistry towards the creation of promising molecules with unique properties.

In the future, the synthesized compounds will be studied for their biological activity by computer prediction and in vivo: analgesic action, neuroprotective activity, antiviral and antimicrobial action.

Aim

The aim of the work was to create a series of 4-amino-2-((R_1,R_2-amino)methyl)-5-((2-,3-,4)-fluorophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones as a promising source for the preparation of biologically active substances.

Materials and methods

The structure of the target compounds has been formed using well-known methods of organic chemistry. The starting materials used were 2-,3-,4-fluorophenyl-4-amino-1,2,4-triazol-3-thiones, which had been previously obtained. The first stage of the work involved the temporary protection of the amino group with a tert-butoxycarbonyl group. The second stage of the work involved the realization of Mannich reactions involving primary and secondary amines. The reaction was carried out with formalin in an alcohol-dioxane medium. The products of the chemical transformation have been recrystallized in methanol. The third stage of the work was based on the removal of Boc protection, which was realized using hydrochloric acid in a dioxane medium.

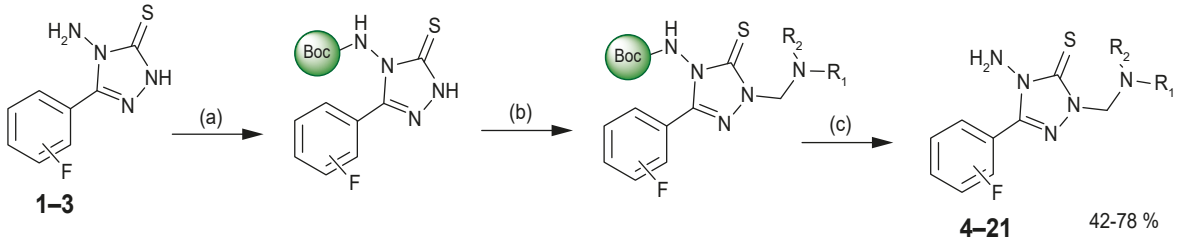
The structures of all synthesized substances have been determined by ^{1}H NMR spectroscopy and elemental analysis. The individuality of the compounds has been confirmed by high-performance liquid chromatography.

Taking into account the above fact, we developed a new strategy for the synthesis of Mannich bases based on new 4-amino-2-((R_1,R_2-amino)methyl)-5-((2-,3-,4)-fluoro-phenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones (**1–3**, *Fig. 1*) and confirmed their structure. We used previously synthesized compounds **1**, **2**, **3** *(Fig. 1)* [10] as starting compounds.

4-Amino-2-((R_1*-,*R_2*-amino)methyl)-5-((2-,3-,4)-fluorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thiones (4–21).* 10 mmol of protected *tert*-butyl(1-((R_1,R_2-amino)methyl)-3-((2-,3-,4)-fluorophenyl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl)carbamate was dissolved in a solution of dioxane with 4 M hydrochloric acid (1.25 equiv.) and stirred at room temperature for 2 h. The solvent was distilled off in a rotary evaporator, washed with water and recrystallized from methanol.

Results

The success of the reaction and formation of Mannich bases is evidenced by the results of ^{1}H NMR spectroscopy *(Fig. 2)*. In the spectrum, the characteristic signals of the methyl residue of the aliphatic amine are observed in a strong field at



a. Boc_2O, $NaHCO_3$, dioxane, r.t., 12–24 h
b. R_1NHR_2, HCHO, EtOH-dioxane
c. 4н HCl/dioxane

Fig. 1. Synthesis of Mannich bases using protection of the amino group.

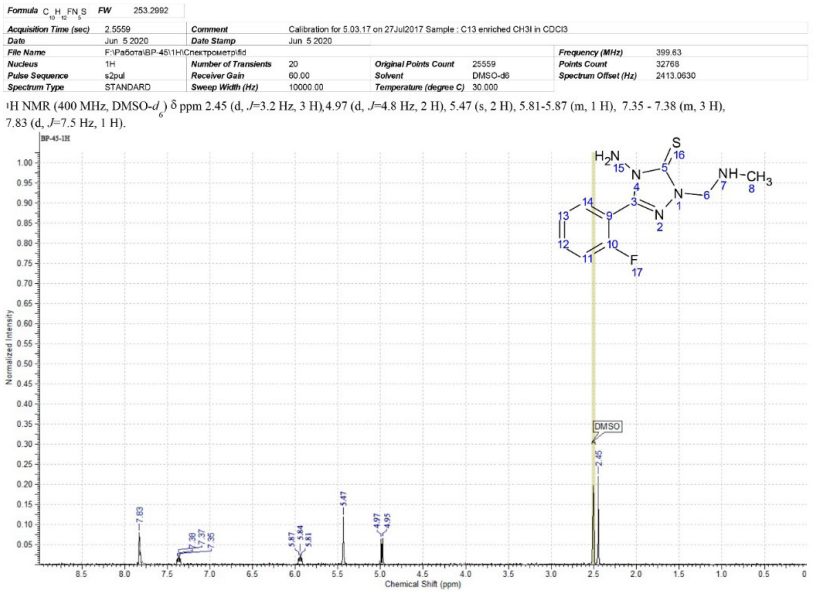


Fig. 2. ^{1}H NMR spectrum of 4-amino-5-(2-fluorophenyl)-2-((methylamino)methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (4).

2.49 ppm. The signal of the protons of the secondary amino group is recorded as a complex multiplet at 5.87–5.81 ppm. The signal of the methylene group from formaldehyde in the Mannich base resonates at 4.97 ppm. in the form of a doublet.

Studying the values of the chemical shift signals for the phenyl ring indicates that the fluorine atom exerts an acceptor effect and shifts the aromatic range of signals slightly into the weak field in the form of doublets and multiplets. Substances are individual crystalline compounds of white or yellow color, insoluble in water, soluble in organic solvents. The structure of the compounds was proven using spectral methods of analysis, and their individuality – chromatographically.

4-Amino-5-(2-fluorophenyl)-2-((methylamino)methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (4). Yield 63 %, yellow cryst. connection, T. pl. 143–145 °C. 1H NMR spectrum, δ, ppm (J, Hz): 7.83 (d, J = 7.5, 1H), 7.38–7.35 (m, 3H), 5.87–5.81 (m, 1H), 5.47 (s, 2H), 4.97 (d, J = 4.8, 2H), 2.45 (d, J = 3.2, 3H). Found, %: C 47.46; H 4.72; N 27.63; S 12.64. $C_{10}H_{12}FN_5S$. Calculated, %: C 47.42; H 4.78; N 27.65; S 12.66.

4-Amino-2-((ethylamino)methyl)-5-(2-fluorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (5). Yield 52 %, yellow cryst. connection, T. pl. 144–146 °C. 1H NMR spectrum, δ, ppm (J, Hz): 7.89 (dd, J = 7.5, 1.6, 1H), 7.35–7.20 (m, 3H), 5.84–5.73 (m, 1H), 5.47 (s, 2H), 5.23 (d, J = 6.7, 2H), 2.92–2.84 (m, 2H), 1,15 (t, J = 5.4, 3H). Found, %: C 49.40; H 5.25; N 26.24; S 11.97. $C_{11}H_{14}FN_5S$. Calculated, %: C 49.42; H 5.28; N 26.20; S 11.99.

4-Amino-2-((diethylamino)methyl)-5-(2-fluorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (6). Yield 59 %, yellow cryst. connection, T. pl. 138–140 °C. 1H NMR spectrum, δ, ppm (J, Hz): 7.90 (dd, J = 7.6, 1.5, 1H), 7.54–7.35 (m, 3H), 5.50 (s, 2H), 4.98 (s, 2H), 2.80–2.74 (m, 4H), 1.14 (t, J = 4.1, 6H). Found, %: C 52.83; H 6.11; N 23.76; S 10.87. $C_{13}H_{18}FN_5S$. Calculated, %: C 52.86; H 6.14; N 23.71; S 10.85.

4-Amino-5-(2-fluorophenyl)-2-(((2-hydroxyethyl)amino)methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (7). Yield 57 %, yellow cryst. connection, T. pl. 125–127 °C. 1H NMR spectrum, δ, ppm (J, Hz): 7.90 (dd, J = 7.5, 1.6, 1H), 7.48–7.21

(m, 3H), 5.84–5.76 (m, 1H), 5.50 (s, 2H), 5.28 (d, J = 6.2, 2H), 4.67 (t, J = 6.3, 1H), 3.72–3.64 (m, 2H), 3.01 (q, J = 7.2, 2H). Found, %: C 46.66; H 4.91; N 24.77; S 11.30. $C_{11}H_{14}FN_5OS$. Calculated, %: C 46.63; H 4.98; N 24.72; S 11.32.

4-Amino-2-((bis(2-hydroxyethyl)amino)methyl)-5-(2-fluorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (8). Yield 51 %, yellow cryst. connection, T.pl. 145–147 °C. 1H NMR spectrum, δ, m.h. (J, Hz): 7.82–7.57 (m, 4H), 5.48 (s, 2H), 5.09 (s, 2H), 4,49 (t, J = 7.5 Hz, 2H), 3.74–3.66 (m, 4H), 2.78 (t, J = 6.6, 4H). Found, %: C 47.64; H 5.51; N 21.41; S 9.74. $C_{13}H_{18}FN_5O2S$. Calculated, %: C 47.69; H 5.54; N 21.39; S 9.79.

4-Amino-5-(2-fluorophenyl)-2-(morpholinomethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (9). Yield 42 %, white cryst. connection, T. pl. 126–128 °C. 1H NMR spectrum, δ, m.h. (J, Hz): 7.54–7.24 (m, 4H), 5.49 (s, 2H), 5.09 (s, 2H), 3,59 (dd, J = 7.4, 4.7, 4H), 2.76 (dd, J = 7.5, 4.8, 4H). Found, %: C 50.41; H 5.24; N 22.68; S 10.32. $C_{13}H_{16}FN_5OS$. Calculated, %: C 50.47; H 5.21; N 22.64; S 10.36.

4-Amino-5-(3-fluorophenyl)-2-((methylamino)methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (10). Yield 59 %, yellow cryst. connection, T.pl. 150–152 °C. 1H NMR spectrum, δ, ppm (J, Hz): 7.72–7.65 (m, 2H), 7.50–7.42 (m, 1H), 7.34–7.25 (m, 1H), 6.02–5.95 (m, 1H), 5.46 (s, 2H), 4.97 (d, J = 4.9, 2H), 2.49 (d, J = 3,2, 3H). Found, %: C 47.48; H 4.72; N 27.61; S 12.63. $C_{10}H_{12}FN_5S$. Calculated, %: C 47.42; H 4.78; N 27.65; S 12.66.

4-Amino-2-((ethylamino)methyl)-5-(3-fluorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (11). Yield 63 %, yellow cryst. connection, T. pl. 154–156 °C. 1H NMR spectrum, δ, m.h. (J, Hz): 7.78–7.70 (m, 2H), 7.65 (t, J = 2.1 Hz, 1H), 7.46–7.36 (m, 1H), 6.20–6.09 (m, 2H), 5.46 (s, 2H), 5.23 (d, J = 6.8, 2H), 2.99–2.91 (m, 2H), 1.15 (t, J = 5.4, 3H). Found, %: C 49.40; H 5.33; N 26.21; S 11.92. $C_{11}H_{14}FN_5S$. Calculated, %: C 49.42; H 5.28; N 26.20; S 11.99.

4-Amino-2-((diethylamino)methyl)-5-(3-fluorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (12). Yield 68 %, yellow cryst. connection, T. pl. 158–160 °C. 1H NMR spectrum, δ, ppm (J, Hz): 7.72–7.64 (m, 2H), 7.51–7.47 (m, 1H), 7.34–7.27 (m, 1H), 5.49 (s, 2H), 4.97 (s, 2H), 2.74 (q, J = 4.2, 4H), 1.14 (t, J = 4.1, 6H). Found, %: C 52.89; H 6.11; N 23.73; S 10.81. $C_{13}H_{18}FN_5S$. Calculated, %: C 52.86; H 6.14; N 23.71; S 10.85.

4-Amino-5-(3-fluorophenyl)-2-(((2-hydroxyethyl)amino)methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (13). Yield 58 %, yellow cryst. connection, T. pl. 188–190 °C. 1H NMR spectrum, δ, ppm (J, Hz): 7.72–7.64 (m, 2H), 7.52–7.46 (m, 1H), 7.34–7.26 (m, 1H), 6.33–6.29 (m, 1H), 5.50 (s, 2H), 5.28 (d, J = 6.2, 2H), 4.67 (t, J = 6.3, 1H), 3.64 (t, J = 7.3, 2H), 3.09–3.01 (m, 2H). Found, %: C 46.67; H 4.93; N 24.77; S 11.30. $C_{11}H_{14}FN_5OS$. Calculated, %: C 46.63; H 4.98; N 24.72; S 11.32.

4-Amino-2-((bis(2-hydroxyethyl)amino)methyl)-5-(3-fluorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (14). Yield 55 %, yellow cryst. connection, T. pl. 186–188 °C. 1H NMR spectrum, δ, ppm (J, Hz): 7.73–7.64 (m, 2H), 7.48–7.41 (m, 1H), 7.33–7.26 (m, 1H), 5.46 (s, 2H), 5.05 (s, 2H), 4.49 (t, J = 7.5, 2H), 3.66 (t, J = 7.7, 4H), 2.78 (t, J = 6.6 Hz, 4H). Found, %: C 47.75; H 5.61; N 15.42; S 9.72. $C_{13}H_{18}FN_5O_2S$. Calculated, %: C 47.69; H 5.54; N 15.48; S 9.79.

4-Amino-5-(3-fluorophenyl)-2-(morpholinomethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (15). Yield 46 %, white cryst. connection, T. pl. 168–170 °C. 1H NMR spectrum, δ, ppm (J, Hz): 7.73–7.65 (m, 2H), 7.52–7.44 (m, 1H), 7.27–7.30 (m, 1H), 5.46 (s, 2H), 5.08 (s, 2H), 3.59 (dd, J = 7.4, 4.7, 4H), 2.76 (dd, J = 7.5, 4,8, 4H). Found, %: C 50.43; H 5.26; N 22.61; S 10.32. $C_{13}H_{16}FN_5OS$. Calculated, %: C 50.47; H 5.21; N 22.64; S 10.36.

4-Amino-5-(4-fluorophenyl)-2-((methylamino)methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (16). Yield 67 %, yellow cryst. connection, T. pl. 185–187 °C. 1H NMR spectrum, δ, ppm (J, Hz): 7.95–7.87 (m, 2H), 7.27–7.19 (m, 2H), 5.95 (m, 1H), 5.47 (s, 2H), 4.97 (d, J = 4.9, 2H), 2.49 (t, J = 3.2, 3H). Found, %: C 47.48; H 4.72; N 27.69; S 12.64. $C_{10}H_{12}FN_5S$. Calculated, %: C 47.42; H 4.78; N 27.65; S 12.66.

4-Amino-5-(4-fluorophenyl)-2-((methylamino)methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (16). Yield 67 %, yellow crystals. connection, T. pl. 185–187 °C. 1H NMR spectrum, δ, ppm (J, Hz): 7.95–7.87 (m, 2H), 7.27–7.19 (m, 2H), 5.95 (m, 1H), 5.47 (s, 2H), 4.97 (d, J = 4.9, 2H), 2.49 (t, J = 3.2, 3H). Found, %: C 47.48; H 4.72; N 27.69; S 12.64. $C_{10}H_{12}FN_5S$. Calculated, %: C 47.42; H 4.78; N 27.65; S 12.66.

4-Amino-2-((diethylamino)methyl)-5-(4-fluorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (18). Yield 56 %, yellow cryst. connection, T. pl. 178–180 °C. 1H NMR spectrum, δ, ppm (J, Hz): 8.00–7.92 (m, 2H), 7.30–7.22 (m, 2H), 5.50 (s, 2H), 4.95 (s, 2H), 2.74 (q, J = 4.2, 4H), 1.14 (t, J = 4.1, 6H). Found, %: C 52.83; H 6.11; N 23.79; S 10.84. $C_{13}H_{18}FN_5S$. Calculated, %: C 52.86; H 6.14; N 23.71; S 10.85.

4-Amino-5-(4-fluorophenyl)-2-(((2-hydroxyethyl)amino)methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (19). Yield 66 %, yellow cryst. connection, T. pl. 188–190 °C. 1H NMR spectrum, δ, ppm (J, Hz): 8.00–7.93 (m, 2H), 7.28–7.20 (m, 2H), 6.29 (m, 1H), 5.50 (s, 2H), 5.28 (d, J = 6.2 Hz, 2H), 4.67 (t, J = 6.3, 1H), 3.64 (t, J = 7.3, 2H), 3.01 (q, J = 7.2, 2H). Found, %: C 46.61; H 5.02; N 24.76; S 11.30. $C_{11}H_{14}FN_5OS$. Calculated, %: C 46.63; H 4.98; N 24.72; S 11.32.

4-Amino-5-(4-fluorophenyl)-2-(((2-hydroxyethyl)amino)methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (19). Yield 66 %, yellow crystals. connection, T. pl. 188–190 °C. 1H NMR spectrum, δ, ppm (J, Hz): 8.00–7.93 (m, 2H), 7.28–7.20 (m, 2H), 6.29 (m, 1H), 5.50 (s, 2H), 5.28 (d, J = 6.2 Hz, 2H), 4.67 (t, J = 6.3, 1H), 3.64 (t, J = 7.3, 2H), 3.01 (sq, J = 7.2, 2H). Found, %: C 46.61; H 5.02; N 24.76; From 11.30. $C_{11}H_{14}FN_5OS$. Calculated, %: C 46.63; H 4.98; N 24.72; S 11.32.

4-Amino-5-(4-fluorophenyl)-2-(morpholinomethyl)-2,4-dihydro-3H-1,2,4-tri-azole-3-thione (21). Yield 76 %, white cryst. connection, T. pl. 178–180 °C. 1H NMR spectrum, δ, ppm (J, Hz): 7.91–7.83 (m, 2H), 7.29–7.21 (m, 2H), 5.46 (s, 2H), 5.08 (s, 2H), 3.59 (dd, J = 7.4, 4.7, 4H), 2.76 (dd, J = 7.5, 4.8, 4H). Found, %: C 50.43; H 5.29; N 21.98; S 10.22. $C_{13}H_{16}FN_5OS$. Calculated, %: C 50.47; H 5.21; N 22.64; S 10.36.

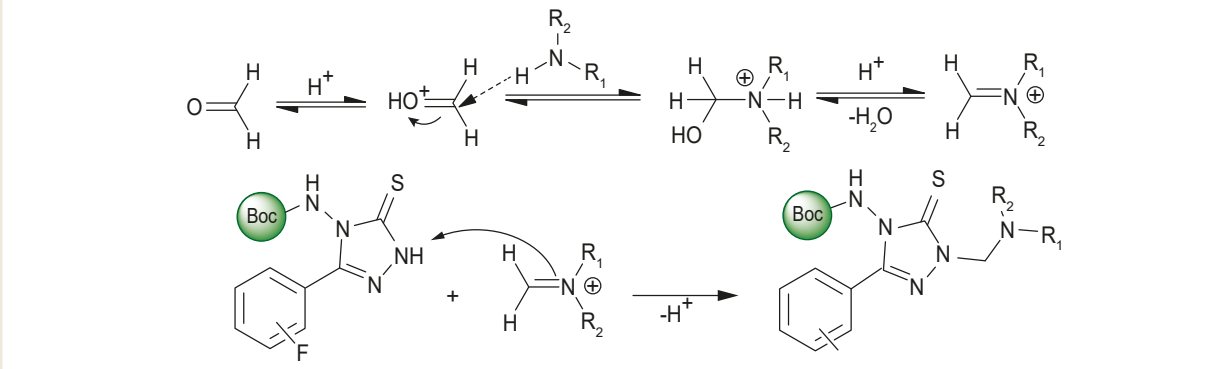


Fig. 3. Potential mechanism of the Mannich reaction in the series 4-amino-2-((R_1,R_2-amino)methyl)-5-((2-, 3-, 4)-fluorophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones.

Discussion

The Mannich reaction mechanism begins with the formation of an iminium ion from an amine and formaldehyde. The reaction mechanism begins with the nucleophilic attack of the Nitrogen atom on the carbonyl Carbon with the formation of an intermediate Schiff base, which acts as an electrophile and reacts with the 1,2,4-triazole heterocycle and leads to the Mannich product due to an elegant and powerful transformation *(Fig. 3)*.

Conclusions

1. A new strategy for the synthesis of Mannich bases based on new 4-amino-2-((R_1,R_2-amino)methyl)-5-((2-,3-,4)-fluorophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones.

2. The synthesis of new 4-amino-2-((R_1-,R_2-amino) methyl)-5-((2-,3-,4-fluorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thiones, the structure of the compounds was proven using spectral methods of analysis, and their individuality was confirmed chromatographically.

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