CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS AND BIOLOGICALLY ACTIVE SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

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RESEARCH ARTICLE

Design and synthesis of 4-nitroimidazole derivatives with potential antitubercular activity

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Abstract

Objectives. *To develop the procedures for synthesis of hybrid molecules with potential antitubercular activity containing heterocyclic cores of 4-nitroimidazole and 1,3,4-thiadiazole within the framework of a double-drug strategy and predict bioactivity of target structures and drug-likeness physicochemical parameters.*

Methods. *Target compounds were prepared by classical organic synthesis methods. The structure of the obtained compounds was characterized by melting points, ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, and high-resolution mass spectrometry. The calculation of the physicochemical parameters of the target compounds and prediction of their biological activity were carried out using publicly available software for cheminformatics and molecular modeling.*

Results. *Acylation of propargylamine with (2-methyl-4-nitro-1H-imidazol-1-yl)acetic and (4-nitro-1H-imidazol-1-yl)acetic acids provided the corresponding amides, which were cyclized with seven different benzylamines in the presence of zinc triflate. In this way, seven new compounds were obtained at 20–30% yields. Ten arylamines were acylated with chloroacetyl chloride and the resulting chloroacetamides were converted into corresponding thio-oxahydrazides by the Willgerodt–Kindler reaction. Following acylation by (4-nitro-1H-imidazol-1-yl)acetic acid, these compounds were converted into the target hybrid imidazolyl-thiadiazoles at 29–54% yields.*

Conclusions. *Two series of new heterocyclic compounds with a hybrid structure including a privileged 4-nitroimidazole moiety linked to the second heterocycle, imidazole, or thiadiazole, were obtained. The synthesis and characterization of compounds by physicochemical methods was aimed at searching for anti-tuberculosis activity. The bioactivity potential of target compounds was demonstrated by preliminary calculations performed using public prognostic programs.*

Keywords: *nitroimidazoles, biimidazoles, 1,3,4-thiadiazoles, N-propargylamides, thiosemicarbazides, zinc triflate*

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НАУЧНАЯ СТАТЬЯ

Дизайн и синтез производных 4-нитроимидазола с потенциальной антитуберкулезной активностью

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Аннотация

Цели. *Разработка синтеза гибридных молекул с потенциальной противотуберкулезной активностью, содержащих гетероциклические системы 4-нитроимидазола и 1,3,4-тиадиазола, в рамках стратегии «double drug». Анализ соответствия их расчетных физико-химических параметров интервалам значений для лекарственно-подобных («drug-likeness») соединений.*
Методы. *Целевые соединения были получены классическими методами органического синтеза. Структура полученных соединений была охарактеризована температурами плавления, спектроскопией ядерного магнитного резонанса ^{1}H и ^{13}C, масс-спектрометрией высокого разрешения. Расчет физико-химических параметров целевых соединений и прогнозирование их биологической активности проводили с использованием общедоступного программного обеспечения для хемоинформатитки и молекулярного моделирования.*
Результаты. *Ацилированием пропаргиламина (2-метил-4-нитро-1Н-имидазол-1-ил)уксусной и (4-нитро-1Н-имидазол-1-ил)уксусной кислотами были получены пропаргиламиды, которые циклизовали с 7 различными бензиламинами в присутствии трифлата цинка. Таким способом с выходами 20–30% от теоретического была получена серия из 7 новых 2-[(4-нитро-1Н-имидазол-1-ил)метил]-1-бензил-5-метил-1Н-имидазолов. 10 ариламинов*

были ацилированы хлорацетилхлоридом. Полученные хлорацетамиды реакцией Вильгеродта–Киндлера превратили в соответствующие тиооксагидразиды. Эти соединения после ацилирования (4-нитро-1Н-имидазол-1-ил)уксусной кислотой были превращены циклодегидратацией в целевые гибридные имидазолил-тиадиазолы, с выходами 29–54%.
Выводы. *Получены две серии новых гетероциклических соединений с гибридной структурой, включающей привилегированный фрагмент 4-нитроимидазола, соединенный алкильным линкером со вторым гетероциклом – имидазолом или тиадиазолом. Соединения сконструированы с целью поиска противотуберкулезной активности, синтезированы и охарактеризованы физико-химическими методами. Предварительные расчеты, выполненные с помощью общедоступных прогностических программ, показали возможный потенциал биологической активности целевых структур.*

Ключевые слова: *нитроимидазолы, биимидазолы, 1,3,4-тиадиазолы, N-пропаргиламиды, тиосемикарбазиды, трифлат цинка*

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INTRODUCTION

One of the most studied structures in medicinal chemistry comprises the imidazole heterocyclic system. Many drugs that are currently on the market or in the process of being developed are based on an imidazole core [1]. Imidazole derivatives are present among antibiotic, antiviral and anticancer drugs, as well as antiprotozoal agents and many other medicinal compounds. These compounds play an important role in the fight against tuberculosis, a socially significant infection that has recently created increasingly serious problems for public health due to the spread of multidrug-resistant strains. Delamanid (**1**) was approved for the treatment of antibiotic-resistant forms of tuberculosis in 2014; another imidazole derivative, Pretomanid (PA-824) (**2**), is currently undergoing phase III clinical trials [2]. Both structures are based on the heterocyclic 4-nitroimidazole system (Fig. 1). 5-Nitroimidazoles have been used antibacterial and antiprotozoal agents [3] since the 1960s; in this connection, it is sufficient to mention the well-known metronidazole (**3**) and ornidazole (**4**) variants. Due to the less well-developed

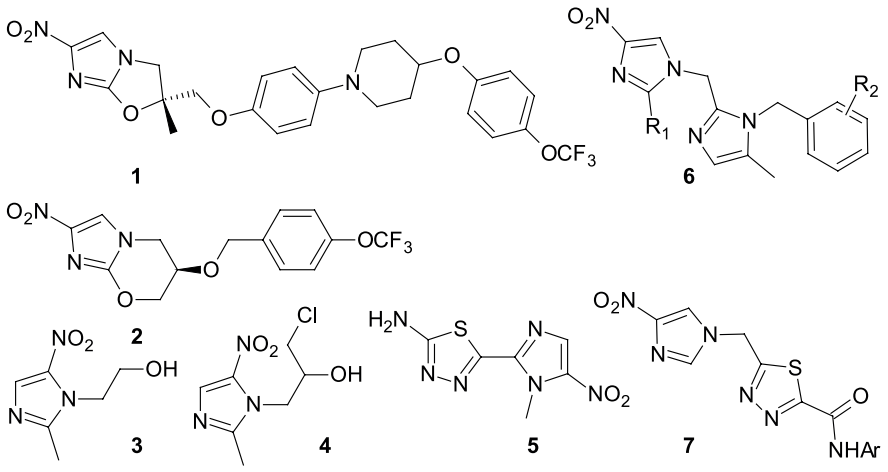


Fig. 1. Structures of nitroimidazole drugs **1**–**5** and synthesized compounds **6**, **7**.

approaches to the synthesis of these substances, the activity of 4-nitroimidazoles only became the subject of studies more recently. The mechanisms of action and biological targets of nitroimidazoles are very diverse. At the first stage of metabolism, cell enzyme systems reduce the nitro group to an amine, while aminoimidazoles inhibit the synthesis of DNA and proteins. Some drugs block mitochondrial oxidation processes to deplete the cell structure [4].

Another example of a privileged structure is the 1,3,4-thiadiazole system. The biological activity of 1,3,4-thiadiazole derivatives is very diverse [5]. Among these substances are antimicrobial, antiprotozoal and antituberculosis agents [6] with high pharmacological potential, as well as registered drugs, for example, megazole with antitrypanosomal activity (**5**). However, the mechanisms of action of these compounds have been much less studied. One of the recent publications suggests inhibition of one of the key enzymes of fatty acid synthesis, enoyl-ACP reductase (EC 1.3.1.9) as comprising such a mechanism [7]. Nevertheless, the very nature of the electron-deficient azole cycle suggests the possibility of effective binding to a wide variety of targets; therefore, other reasons for the antimicrobial action are also likely, for example, inhibition of inosine monophosphate dehydrogenase (EC 1.1.1.205), a key enzyme in the *de-novo* synthesis of purine nucleotides [2].

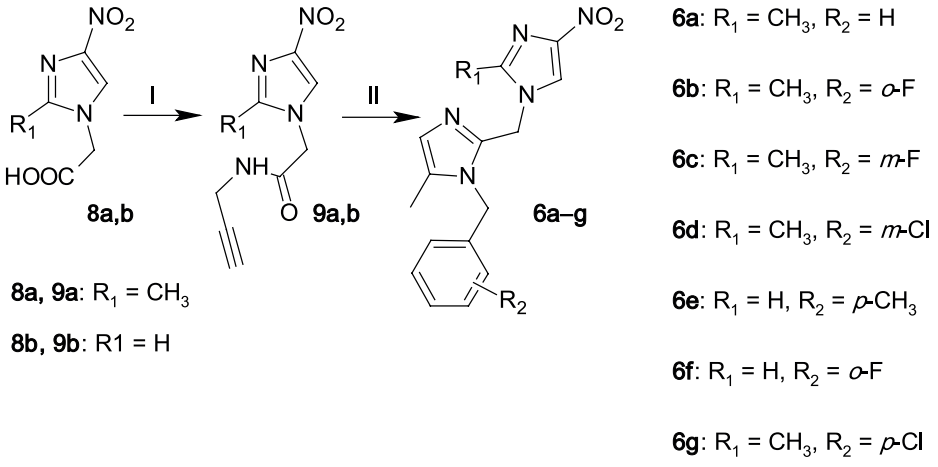
The aim of the present work is to develop the procedures for synthesis of hybrid molecules containing such heterocyclic systems within the framework of a "double-drug strategy". Such a strategy, which is widely used in the search for new active structures [8], was previously used by us to obtain active derivatives of the 5-nitrofuran pharmacophore [9]. The design of the target structures included an analysis of the correspondence of their calculated physicochemical parameters to the ranges of values for drug-likeness compounds. The structures of the synthesized compounds **6**, **7** are shown in Figs. 1.

RESULTS AND DISCUSSION

The first series of compounds **6a–g** was designed similarly to several previously described compounds offering high antituberculosis activity [10, 11]. The structures of the prototype compounds include 2 imidazole cycles attached via an alkyl linker. The advantages of such a structure from the point of view of biological activity are considered in review papers [2, 12]. The inclusion of a flexible linker between pharmacophore fragments presumably increases the likelihood of the molecule binding to different target sites.

Target compounds **6a–g** were synthesized by the zinc promoted reaction of propargylamides **9a** and **9b** with primary amines [13–15] (Scheme 1).

Propargylamides **9a** and **9b** were obtained by acylation of propargylamine with (2-methyl-4-nitro-1*H*-imidazol-1-yl)acetic (**8a**) and (4-nitro-1*H*-imidazol-1-yl)acetic (**8b**) acids in dimethylformamide (DMF) in the presence of 1,1'-carbonyldiimidazole (CDI). The yield of propargylamides was 64% and 53%, respectively. Next, propargylamides **9a** and **9b** were heated for 6 h in toluene with the corresponding benzylamines in the presence of zinc triflate; the reaction product was isolated by silica gel column chromatography. Following isolation



Scheme 1. Synthesis of compounds **6a–g**.
Reagents and conditions: (I) carbonyldiimidazole (CDI), propargyl amine, dimethylformamide (DMF), 16 h; (II) $Zn(CF_3SO_3)_2$, $R_2–PhCH_2NH_2$, toluene, reflux, 6 h.

and purification, the yields of compounds **6a–6g** varied in the range of 20–30% of the theoretical maximum. The structure of the obtained compounds was confirmed by ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy.

Hybrid imidazolyl-thiadiazoles **7** include two heterocyclic nuclei linked by a methylene linker—4-nitroimidazole and thiadiazole—as well as a peripheral aryl group. The general structure of **7** is similar to the compounds of series **6** and the structure of megazole **5**; its isosteric compounds having an oxadiazole ring exhibit significant antibacterial activity [16]. Series **7a–j** was obtained using a 5-step scheme starting with the acylation of arylamines **10** with chloroacetyl chloride [17] (Scheme 2).

In the next step, chloroacetamides **11** were used without additional purification following treatment in the Willgerodt–Kindler reaction with elemental sulfur and morpholine, and then with hydrazine hydrate. Thus, without isolation of intermediate thiooxamides **12**, compounds **13a–13j** were obtained, which were purified by crystallization from ethanol and characterized by physicochemical methods. The thio-oxahydrazides **13** were acylated with commercially available (4-nitro-1*H*-imidazol-1-yl)-acetic acid and then subjected to cyclodehydration in glacial acetic acid. The yields of target arylamides **7a–7j** after column chromatography were 29–54%. Compounds **7a-j** were characterized by melting points, ^{1}H- and ^{13}C-NMR spectra.

The calculation of the physicochemical parameters of the target compounds using the publicly available Molinspiration[1] and SwissADME[2] software demonstrated a correspondence between their lipophilicity and molecular weight ratios with the Lipinski criteria [18] for drug-likeness compounds (Fig. 2).

The prediction of the biological activity of structures **6** and **7** using the Molinspiration Virtual Screening Toolkit shows additional significant similarity with known GPCR ligands, representing the bulk of drug-active compounds. On this basis, positive results of the proposed biological screening can be expected.

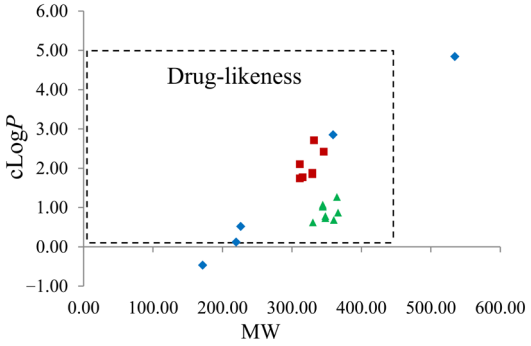
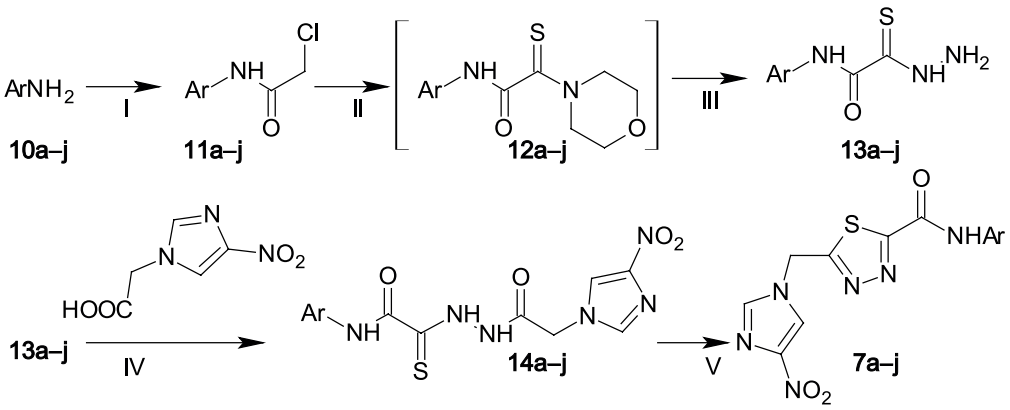


Fig. 2. Calculated physicochemical parameters of the target compounds:
♦ compounds 2–5; ■ compounds 6; ▲ compounds 7.
MW — molecular weight; cLogP — average lipophilicity value calculated from five predictions using the standard 1-octanol–water system.



Ar: Ph (**a**); 3,4-F-Ph (**b**); 4-MeOPh (**c**); 3-Cl-Ph (**d**); 4-Me-Ph (**e**);
2,4-F-Ph (**f**); 2-F-Ph (**g**); 2-Me-Ph (**h**); 4-F-Ph (**i**); 3-Me-Ph (**j**)

Scheme 2. Synthesis of 5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxyaryl amides(**7a–j**).
Reagents and conditions: (I) Et_3N, CH_2Cl_2; (II) S_8, morpholine, Et_3N, DMF, room temperature (r.t. is assumed to be equal to 25°C), 16 h; (III) $N_2H_4 \cdot H_2O$, DMF, r.t., 16 h; (IV) CDI, DMF, r.t., 16 h; (V) AcOH, reflux, 0.5 h.

[1] Molinspiration Cheminformatics. URL: https://www.molinspiration.com. Accessed December 13, 2022.
[2] SwissADME. URL: http://www.swissadme.ch. Accessed December 13, 2022.

EXPERIMENTAL

All reactions were carried out in glassware preliminarily dried at 140°C under a nitrogen atmosphere. Melting points as determined with a C-520 melter (*Büchi*, Switzerland) were not corrected. Analytical thin layer chromatography (TLC) was performed on Sorbfil plates (*IMID*, Russia) using the corresponding ethyl acetate/hexane and chloroform/methanol solvent systems. Compounds were visualized using shortwave ultraviolet light. ^{1}H and ^{13}C NMR spectra were recorded on a DPX-300 spectrometer (*Bruker*, Germany) in DMSO-d_6 and $CDCl_3$ using tetramethylsilane as an internal standard. Mass spectra of the final compounds were recorded on an Agilent 6210 TOF time-of-flight mass spectrometer (*Agilent*, USA) with electrospray ionization (ESI-MS). All reagents and solvents were obtained from commercial sources and used without further purification.

General procedure for the synthesis of compounds 9a–b

To 16.2 mmol of carboxylic acid **8** in 25 mL of dry DMF was added 17.8 mmol of CDI, and the mixture was left to stir at room temperature for 30 min. Then 17.8 mmol of propargylamine was added and left to stir at room temperature for 16 h. The reaction mixture was poured into water (150 mL) and extracted with ethyl acetate. The organic phase was washed with 5% K_2CO_3 aqueous solution (2 × 20 mL), dried over anhydrous Na_2SO_4, and evaporated on a rotary evaporator under vacuum. The residue was suspended in diethyl ether; the precipitate was filtered off.

2-(2-methyl-4-nitro-1*H*-imidazol-1-yl)-*N*-prop-2-yn-1-ylacetamide 9a

Yield of 2.3 g (64%), light yellow crystals, $T_{m.p.}$ = 150–151°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 8.80 (t, *J* = 5.1 Hz, 1H), 8.28 (s, 1H), 4.80 (s, 2H), 3.93 (dd, *J* = 5.3, 2.4 Hz, 2H), 3.19 (t, *J* = 2.4 Hz, 1H), 2.25 (s, 3H).

2-(4-nitro-1*H*-imidazol-1-yl)-*N*-prop-2-yn-1-ylacetamide 9b

Yield of 1.3 g (53.4%), orange crystals, $T_{m.p.}$ = 139–140°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 8.76 (t, *J* = 5.1 Hz, 1H), 8.33 (s, 1H), 7.80 (s, 1H), 4.86 (s, 2H), 3.93 (dd, *J* = 5.3, 2.4 Hz, 2H), 3.19 (t, *J* = 2.4 Hz, 1H).

General procedure for the synthesis of compounds 6a-g

To 0.90 mmol of propargylamide **9** in 20 mL of toluene, 1.08 mmol of the corresponding benzylamine and 0.2 mmol of $Zn(CF_3SO_3)_2$ were added, and the mixture was boiled for 8 h with distillation of water. The reaction mixture was evaporated, the residue was dissolved in ethyl acetate and washed with a 5% aqueous solution of K_2CO_3 (2 × 15 mL), dried over anhydrous Na_2SO_4, and evaporated on a rotary evaporator under vacuum. The residue was subjected to silica gel column chromatography, eluting with chloroform, increasing the polarity by adding methanol from 0% to 20%. Fractions containing the target product were combined and evaporated.

1-[(1-benzyl-5-methyl-1*H*-imidazol-2-yl)-methyl]-2-methyl-4-nitro-1*H*-imidazole 6a

Yield of 110 mg (26%), orange crystals, $T_{m.p.}$ = 119–120°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.37 (s, 1H), 7.30–7.27 (m, 1H), 7.26 (d, *J* = 2.0 Hz, 2H), 6.90 (s, 1H), 6.80–6.75 (m, 2H), 5.03 (s, 2H), 4.99 (s, 2H), 2.29 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 146.4, 144.8, 140.0, 135.0, 130.4, 129.4, 128.5, 126.7, 125.2, 119.9, 47.0, 43.7, 13.3, 9.7. ESI-MS: calculated for $[C_{16}H_{18}N_5O_2]^+$ 312.1461, found 312.1453.

1-[(1-(2-fluorobenzyl)-5-methyl-1*H*-imidazol-2-yl)-methyl]-2-methyl-4-nitro-1*H*-imidazole 6b

Yield of 80 mg (27%), orange crystals, $T_{m.p.}$ = 138–139°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.38 (s, 1H), 7.27–7.19 (m, 2H), 7.08–7.02 (m, 1H), 7.01–6.93 (m, 1H), 6.91 (s, 1H), 5.09 (s, 2H), 5.07 (s, 2H), 2.33 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 159.6 (d, *J* = 246.4 Hz), 146.3, 144.7, 139.9, 130.6 (d, *J* = 8.2 Hz), 130.4, 126.6, 126.5 (d, *J* = 3.3 Hz), 125.1 (d, *J* = 3.6 Hz), 122.0 (d, *J* = 14.0 Hz), 119.6, 115.9 (d, *J* = 20.5 Hz), 43.5, 41.4 (d, *J* = 5.4 Hz), 13.3, 9.8. ESI-MS: calculated for $[C_{16}H_{17}FN_5O_2]^+$ 330.1366, found 330.1371.

1-[(1-(3-fluorobenzyl)-5-methyl-1*H*-imidazol-2-yl)-methyl]-2-methyl-4-nitro-1*H*-imidazole 6c

Yield of 60 mg (20.2%), orange crystals, $T_{m.p.}$ = 156–157°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.47 (s, 1H), 7.31–7.22 (m, 1H), 6.98 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.94 (s, 1H), 6.57 (broad.d, *J* = 7.7 Hz, 1H), 6.48 (broad.d, *J* = 9.2 Hz, 1H), 5.06 (s, 4H), 2.33 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 163.4 (d, *J* = 249.1 Hz), 146.4, 144.8, 139.9, 137.5 (d, *J* = 7.0 Hz), 131.2 (d, *J* = 8.4 Hz), 130.5, 126.7, 120.7 (d, *J* = 3.0 Hz), 119.8, 115.6 (d, *J* = 21.1 Hz), 112.3 (d, *J* = 22.7 Hz), 46.5 (d, *J* = 1.8 Hz), 43.6, 13.4, 9.7. ESI-MS: calculated for $[C_{16}H_{17}FN_5O_2]^+$ 330.1366, found 330.1362.

1-[(1-(3-chlorobenzyl)-5-methyl-1*H*-imidazol-2-yl)methyl]-2-methyl-4-nitro-1*H*-imidazole 6d

Yield of 80 mg (25.7%), orange crystals, $T_{m.p.}$ = 164–165°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.47

(s, 1H), 7.24 (t, *J* = 6.1 Hz, 2H), 6.94 (s, 1H), 6.74 (broad.s, 1H), 6.68 (broad.d, *J* = 6.5 Hz, 1H), 5.04 (s, 4H), 2.32 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 146.4, 144.8, 139.9, 136.9, 135.7, 130.7, 130.5, 128.8, 126.7, 125.3, 123.3, 119.7, 46.4, 43.6, 13.4, 9.8. ESI-MS: calculated for $[C_{16}H_{17}ClN_5O_2]^+$ 346.1071, found 346.1066.

5-methyl-1-(4-methylbenzyl)-2-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1*H*-imidazole 6e

Yield of 90 mg (30.7%), orange crystals, $T_{m.p.}$ = 110–111°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.45 (s, 1H), 7.28 (s, 1H), 7.04 (broad.d, *J* = 7.6 Hz, 2H), 6.88 (s, 1H), 6.68 (broad.d, *J* = 7.7 Hz, 2H), 5.11 (s, 2H), 5.03 (s, 2H), 2.27 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 147.6, 140.1, 138.4, 137.4, 135.8, 132.2, 130.3, 129.9, 129.2, 126.6, 125.3, 119.6, 46.7, 44.2, 20.9, 9.7. ESI-MS: calculated for $[C_{16}H_{18}N_5O_2]^+$ 312.1461, found 312.1460.

1-(2-fluorobenzyl)-5-methyl-2-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1*H*-imidazole 6f

Yield of 80 mg (24.3%), orange crystals, $T_{m.p.}$ = 132–133°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.59 (s, 1H), 7.33 (s, 1H), 7.26–7.22 (m, 1H), 7.08–7.01 (m, 1H), 6.99–6.92 (m, 1H), 6.90 (s, 1H), 6.40 (t, *J* = 7.7 Hz, 1H), 5.21 (s, 2H), 5.12 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 159.6 (d, *J* = 246.6 Hz), 147.9, 140.1, 135.7, 130.5, 130.3 (d, *J* = 8.1 Hz), 127.0, 126.8 (d, *J* = 3.3 Hz), 125.0 (d, *J* = 3.5 Hz), 122.3 (d, *J* = 14.1 Hz), 119.4, 115.9 (d, *J* = 20.7 Hz), 44.2, 41.3 (d, *J* = 5.1 Hz), 9.7. ESI-MS: calculated for $[C_{15}H_{15}FN_5O_2]^+$ 316.1210, found 316.1222.

1-[(1-(4-chlorobenzyl)-5-methyl-1*H*-imidazol-2-yl)methyl]-2-methyl-4-nitro-1*H*-imidazole 6g

Yield of 70 mg (22.5%), orange crystals, $T_{m.p.}$ = 189–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.47 (s, 1H), 7.29 (s, 1H), 7.26 (s, 1H), 6.92 (s, 1H), 6.74 (d, *J* = 8.3 Hz, 2H), 5.04 (s, 2H), 5.03 (s, 2H), 2.33 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 146.5, 144.9, 139.9, 134.6, 133.5, 130.4, 129.7, 126.8, 126.6, 119.8, 46.5, 43.7, 13.4, 9.7. ESI-MS: calculated for $[C_{16}H_{17}ClN_5O_2]^+$ 346.1071, found 346.1075.

General procedure for the synthesis of compounds 13a-j

5.0 mmol of the corresponding aniline **10** was dissolved in 25 mL of CH_2Cl_2. 5.5 mmol of triethylamine and 5.0 mmol of chloroacetyl chloride were added, and the reaction mixture was stirred at room temperature for 16 h. The triethylammonium chloride precipitate was filtered off and concentrated under vacuum to obtain 2-chloroacetamide **11**, which was further used without further purification.

Triethylamine (32.0 mmol) and morpholine (2.12 mmol) were successively added (dropwise) to a suspension of elemental sulfur (32.0 mmol) in dry DMF (40 mL), and the resulting mixture was stirred for 30 min. Then a solution of 1.0 mmol of 2-chloroacetamide **11** was added and the mixture was left to stir overnight. The mixture was poured into 100 mL of water, the resulting precipitate was filtered off and air dried. Then it was suspended in 100 mL of acetone and the insoluble residue of unreacted sulfur was filtered off and discarded. The filtrate was evaporated to dryness, and the dry residue of thiomorpholide **12** was dissolved in 30 mL of dry DMF, treated with 5 mL of hydrazine hydrate, and stirred for 12 h. The reaction mixture was poured into water, and the pH of the aqueous medium was adjusted to 5.0 with 2 M aqueous HCl. The resulting precipitate was filtered off, washed with water, air dried, and crystallized from ethanol to give analytically pure compounds **13** in the indicated yields.

2-hydrazino-*N*(1)-phenyl-2-thiooxacetamide 13a

Yield of 107 mg (55%), yellow crystals, $T_{m.p.}$ = 152–153°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.21 (s, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 5H), 7.14 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 167.7, 158.4, 137.9, 129.3, 125.0, 120.5.

***N*(1)-(3,4-difluorophenyl)-2-hydrazino-2-thiooxacetamide 13b**

Yield of 175 mg (76%), yellow crystals, $T_{m.p.}$ = 164–165°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.41 (s, 1H), 7.91 (ddd, *J* = 13.0, 7.4, 2.4 Hz, 1H), 7.65–7.55 (m, 1H), 7.43 (dd, *J* = 19.5, 9.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 167.8, 158.9, 149.5 (dd, *J* = 210.8, 12.9 Hz), 146.3 (dd, *J* = 210.4, 13.0 Hz), 135.1 (dd, *J* = 9.1, 3.0 Hz), 117.9 (d, *J* = 17.9 Hz), 117.43 (dd, *J* = 6.1, 3.4 Hz), 109.97 (d, *J* = 21.7 Hz).

2-hydrazino-*N*(1)-(4-methoxyphenyl)-2-thiooxacetamide 13c

Yield of 173 mg (77%), yellow crystals, $T_{m.p.}$ = 168–169°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.10 (s, 1H), 7.66 (t, *J* = 6.2 Hz, 2H), 6.92 (t, *J* = 6.1 Hz, 1H), 3.73 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 167.8, 158.0, 156.6, 131.0, 122.2, 114.4, 55.7.

***N*(1)-(3-chlorophenyl)-2-hydrazino-2-thiooxacetamide 13d**

Yield of 146 mg (64%), yellow crystals, $T_{m.p.}$ = 162–163°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.38 (s, 1H), 7.94 (t, *J* = 2.0 Hz, 1H),

7.73–7.68 (m, 1H), 7.38 (t, J = 8.1 Hz, 1H), 7.20 (dd, J = 7.8, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 167.6, 159.0, 139.5, 133.5, 130.9, 124.7, 120.2, 119.2.

2-hydrazino-*N*(1)-(4-methylphenyl)-2-thiooxacetamide 13e

Yield of 115 mg (55%), yellow crystals, $T_{m.p.}$ = 155–156°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.13 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 167.7, 158.2, 135.4, 134.2, 129.7, 120.5, 21.0.

***N*(1)-(2,4-difluorophenyl)-2-hydrazino-2-thiooxacetamide 13f**

Yield of 164 mg (71%), yellow crystals, $T_{m.p.}$ = 174–175°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.19 (s, 1H), 7.91 (tt, J = 19.2, 9.6 Hz, 1H), 7.41 (ddd, J = 11.5, 9.0, 2.8 Hz, 1H), 7.28–7.04 (m, 1H), 7.19–7.08 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 165.81, 159.5 (dd, J = 244.7, 11.7 Hz), 157.9, 154.6 (dd, J = 248.4, 12.7 Hz), 125.0 (dd, J = 9.7, 2.3 Hz), 122.2 (dd, J = 11.5, 3.7 Hz), 111.9 (dd, J = 22.1, 3.7 Hz), 104.8 (dd, J = 27.1, 23.8 Hz).

***N*(1)-(2-fluorophenyl)-2-hydrazino-2-thiooxacetamide 13g**

Yield of 149 mg (70%), yellow crystals, $T_{m.p.}$ = 172–173°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.26 (s, 1H), 8.05 (ddd, J = 7.8, 5.6, 2.9 Hz, 1H), 7.40–7.29 (m, 1H), 7.28–7.19 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 165.7, 157.5, 154.0 (d, J = 244.9 Hz), 126.6 (d, J = 7.8 Hz), 125.5 (d, J = 10.9 Hz), 125.3 (d, J = 3.6 Hz), 122.8, 116.0 (d, J = 19.0 Hz).

2-hydrazino-*N*(1)-(2-methylphenyl)-2-thiooxacetamide 13h

Yield of 152 mg (73%), yellow crystals, $T_{m.p.}$ = 151–152°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.09 (s, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.25 (dd, J = 13.5, 7.5 Hz, 2H), 7.11 (t, J = 7.4 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 166.8, 157.4, 135.8, 130.9, 130.0, 126.9, 125.8, 122.1, 17.8.

***N*(1)-(4-fluorophenyl)-2-hydrazino-2-thiooxacetamide 13i**

Yield of 132 mg (62%), yellow crystals, $T_{m.p.}$ = 179–180°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.28 (s, 1H), 7.78 (ddd, J = 8.5, 5.2, 2.9 Hz, 1H), 7.23–7.16 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 167.9, 159.2 (d, J = 241.5 Hz), 158.5, 134.4 (d, J = 2.6 Hz), 122.7 (d, J = 8.0 Hz), 115.9 (d, J = 22.4 Hz).

2-hydrazino-*N*(1)-(3-methylphenyl)-2-thiooxacetamide 13j

Yield of 123 mg (59%), yellow crystals, $T_{m.p.}$ = 115–116°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.12 (s, 1H), 7.56 (s, 2H), 7.25 (dd, J = 11.4, 4.8 Hz, 1H), 6.96 (d, J = 7.3 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 167.8, 158.2, 138.6, 137.8, 129.2, 125.8, 120.9, 117.6, 21.6.

General procedure for the synthesis of compounds 7a–j

To 1.07 mmol of (4-nitro-1*H*-imidazol-1-yl) acetic acid **8b** and 25 mL of dry DMF was added 1.18 mmol of CDI and the mixture was left to stir at room temperature for 30 min. Then, 1.18 mmol of the corresponding compound **13** was added and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured into 100 mL of water, the precipitation **14** that formed was filtered off and air dried. Without further purification, thiohydrazide **14** was boiled in 3 mL of glacial acetic acid with 12.8 mmol of succinic anhydride for 30 min, cooled, and poured into 25 mL of water. The resulting precipitation, predominantly consisting of compound **7**, was filtered off and air dried. The precipitation was purified by silica gel column chromatography (eluent, ethyl acetate). Fractions containing target product **7** were combined and exhausted.

5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-*N*-phenyl-1,3,4-thiadiazole-2-carboxamide 7a

Yield of 130 mg (36.7%), orange crystals, $T_{m.p.}$ = 182–183°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.16 (s, 1H), 8.56 (s, 1H), 8.08 (s, 1H), 7.82 (d, J = 8.2 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.17 (t, J = 7.2 Hz, 1H), 5.97 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 168.8, 167.5, 155.9, 147.2, 137.9, 137.6, 128.8, 124.8, 121.9, 120.9, 45.4. ESI-MS: calculated for $[C_{13}H_{11}N_6O_3S]$+ 331.0613, found 331.0621.

***N*-(3,4-difluorophenyl)-5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxamide 7b**

Yield of 180 mg (46%), orange crystals, $T_{m.p.}$ = 208–209°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.45 (s, 1H), 8.57 (s, 1H), 8.08 (s, 1H), 8.00–7.90 (m, 1H), 7.71–7.65 (m, 1H), 7.47 (q, J = 9.3 Hz, 1H), 5.97 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 169.1, 167.0, 156.2, 148.8 (dd, J = 243.7, 13.2 Hz), 147.2, 146.2 (dd, J = 243.4, 12.6 Hz), 137.9, 134.6 (dd, J = 9.0, 3.1 Hz), 121.9, 117.6 (d, J = 18.0 Hz), 117.4 (dd, J = 6.3, 3.4 Hz), 110.0 (d, J = 21.7 Hz), 45.4. ESI-MS: calculated for $[C_{13}H_9F_2N_6O_3S]^+$ 367.0425, found 367.0396.

***N*-(4-methoxyphenyl)-5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxamide 7c**:

Yield of 170 mg (44.1%), orange crystals, $T_{m.p.}$ = 204–205°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.09 (s, 1H), 8.57 (s, 1H), 8.08 (s, 1H), 7.73 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 5.96 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 168.7, 167.7, 156.3, 155.5, 147.2, 138.0, 130.6, 122.5, 122.0, 113.9, 55.3, 45.5. ESI-MS: calculated for $[C_{14}H_{13}N_6O_4S]^+$ 361.0719, found 361.0724.

***N*-(3-chlorophenyl)-5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxamide 7d**

Yield of 110 mg (28.2%), orange crystals, $T_{m.p.}$ = 205–206°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.39 (s, 1H), 8.57 (s, 1H), 8.08 (s, 1H), 7.98 (s, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 5.97 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 169.5, 167.5, 156.7, 147.6, 139.5, 138.4, 133.5, 131.0, 125.0, 122.4, 120.8, 119.7, 45.9. ESI-MS: calculated for $[C_{13}H_{10}ClN_6O_3S]^+$ 365.0224, found 365.0225.

***N*-(4-methylphenyl)-5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxamide 7e**

Yield of 150 mg (40.7%), orange crystals, $T_{m.p.}$ = 215–216°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.07 (s, 1H), 8.55 (d, *J* = 1.2 Hz, 1H), 8.07 (d, *J* = 1.3 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 5.96 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 168.6, 167.5, 155.7, 147.1, 137.8, 135.0, 133.9, 129.1, 121.8, 120.8, 45.4, 20.5. ESI-MS: calculated for $[C_{14}H_{13}N_6O_3S]^+$ 345.0770, found 345.0758.

***N*-(2,4-difluorophenyl)-5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxamide 7f**

Yield of 190 mg (48.5%), orange crystals, $T_{m.p.}$ = 213–214°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.01 (s, 1H), 8.56 (s, 1H), 8.08 (s, 1H), 7.62–7.52 (m, 1H), 7.46–7.35 (m, 1H), 7.15 (t, *J* = 8.4 Hz, 1H), 5.97 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 169.1, 166.5, 160.5 (dd, *J* = 246.0, 11.7 Hz), 156.5, 156.4 (dd, *J* = 251.0, 13.0 Hz), 147.3, 138.1, 128.9 (dd, *J* = 9.9, 2.6 Hz), 122.1, 120.7 (dd, *J* = 12.7, 3.8 Hz), 111.7 (dd, *J* = 22.3, 3.6 Hz), 104.8 (dd, *J* = 26.8, 24.2 Hz), 45.5. ESI-MS: calculated for $[C_{13}H_9F_2N_6O_3S]^+$ 367.0425, found 367.0428.

5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-*N*-(2-fluorophenyl)-1,3,4-thiadiazole-2-carboxamide 7g

Yield of 170 mg (45.6%), orange crystals, $T_{m.p.}$ = 173–174°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.95 (s, 1H), 8.57 (d, *J* = 1.1 Hz, 1H), 8.08 (d, *J* = 1.1 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.36–7.31 (m, 2H), 7.27–7.21 (m, 1H), 5.98 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 169.0, 166.6, 156.2, 155.8 (d, *J* = 248.1 Hz), 147.2, 138.0, 128.1 (d, *J* = 7.8 Hz), 127.2, 124.5 (d, *J* = 3.5 Hz), 124.0 (d, *J* = 12.3 Hz), 122.0, 116.0 (d, *J* = 19.6 Hz), 45.4. ESI-MS: calculated for $[C_{13}H_{10}FN_6O_3S]^+$ 349.0519, found 349.0520.

***N*-(2-methylphenyl)-5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxamide 7h**

Yield of 200 mg (54.3%), orange crystals, $T_{m.p.}$ = 185–186°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.72 (s, 1H), 8.57 (d, *J* = 1.4 Hz, 1H), 8.08 (d, *J* = 1.4 Hz, 1H), 7.39–7.35 (m, 1H), 7.31–7.27 (m, 1H), 7.25–7.20 (m, 2H), 5.97 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 168.6, 167.1, 156.0, 147.2, 137.8, 134.7, 133.5, 130.4, 126.7, 126.3, 126.1, 121.8, 45.3, 17.6. ESI-MS: calculated for $[C_{14}H_{13}N_6O_3S]^+$ 345.0770, found 345.0764.

5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-*N*-(4-fluorophenyl)-1,3,4-thiadiazole-2-carboxamide 7i

Yield of 120 mg (32.2%), orange crystals, $T_{m.p.}$ = 228–229°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.24 (s, 1H), 8.55 (d, *J* = 1.1 Hz, 1H), 8.07 (d, *J* = 1.3 Hz, 1H), 7.88–7.82 (m, 2H), 7.22 (t, *J* = 8.9 Hz, 2H), 5.97 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 168.9, 167.393, 158.990 (d, *J* = 241.8 Hz), 155.9, 147.2, 137.9, 133.9 (d, *J* = 2.6 Hz), 122.8 (d, *J* = 8.0 Hz), 121.9, 115.4 (d, *J* = 22.4 Hz), 45.4. ESI-MS: calculated for $[C_{13}H_{10}FN_6O_3S]^+$ 349.0519, found 349.0533.

***N*-(3-methylphenyl)-5-[(4-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazole-2-carboxamide 7j**

Yield of 110 mg (29.8%), orange crystals, $T_{m.p.}$ = 200–201°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 11.05 (s, 1H), 8.55 (d, *J* = 1.0 Hz, 1H), 8.07 (d, *J* = 0.9 Hz, 1H), 7.67 (s, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 5.96 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 168.8, 167.5, 155.9, 147.2, 138.1, 138.0, 137.5, 128.6, 125.5, 122.0, 121.4, 118.1, 45.4, 21.2. ESI-MS: calculated for $[C_{14}H_{13}N_6O_3S]^+$ 345.0770, found 345.0764.

CONCLUSIONS

In the course of the work, two novel series of heterocyclic compounds having a hybrid structure were obtained, including a preferred fragment of 4-nitroimidazole, which was connected by an alkyl linker with a second heterocycle, imidazole (**6**) or thiadiazole (**7**). The compounds designed as part of a search for anti-tuberculosis activity were synthesized and characterized by

physicochemical methods. Preliminary calculations using publicly available prognostic programs demonstrated the potential biological activity of target structures.

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Authors' contributions

T.S. Vedekhina – conducting experiments;

M.V. Chudinov – the research results analysis and presentation;

A.Yu. Lukin – creating a research concept.

The authors declare no conflicts of interest.

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