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SYNTHESIS OF SUBSTITUTED 5-(THIOPHEN-2-YL)-1H-TETRAZOLES

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Novel N-(5-aryl-2-(*1H*-tetrazol-5-yl)thiophen-3-yl)acetamides were obtained by the acylation of 2-(*1H*-tetrazol-5-yl)-5-aryl-3-aminothiophenes, synthesized by the reaction of 5-aryl-3-aminothiophenes with ammonium azide in the inert atmosphere.

Keywords: tetrazolyl-3-aminothiophenes, [3+2] cycloaddition, acylation.

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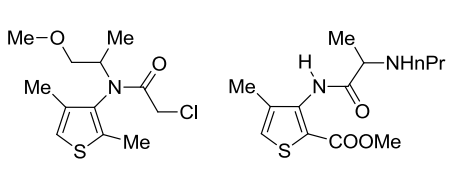
1. Introduction

Drugs based on heterocyclic compounds are widely used in medical practice. Among the heterocyclic compounds, thiophene derivatives occupy a significant place due to the bioisosterity of the thiophene ring to benzene ring and 5-substituted tetrazole moiety is used in pharmaceuticals as carboxylic group bioisosteres. Tetrazole derivatives provoke a considerable interest in recent decades due to their chemical, photophysical and biological activities. At the same time, thiophene derivatives arouse great interest in pharmaceutical chemistry due to a wide range of biological activities. Thus, thiophene and tetrazole cycles are a fragment of many pharmaceutical drugs (articaine, protiofate, oliceridine, valsartan, cefotiam and others), pesticides (dimethanamide).



dimethenamid articaine Valsartan

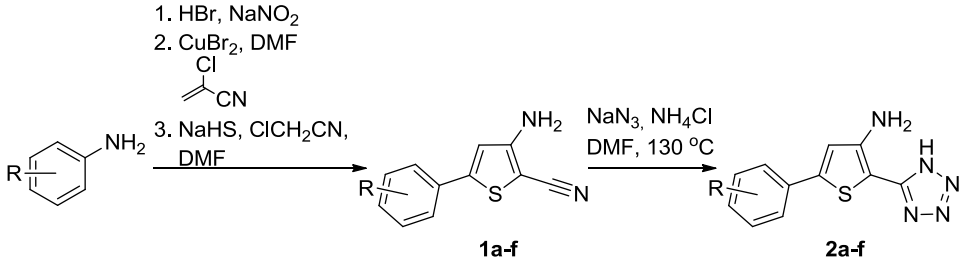
Compounds containing of thiophene and tetrazole cycles are reported as antibacterial nonpeptide antagonists platelet aggregators, antithrombotic agents [0, 2] and nonlinear optical materials [3]. Similarly, these derivatives are well known to exhibit various activities such as anti-inflammatory [4, 5], antibacterial [4–6], anticancer [7–11], antiviral [11], antifungal [12], inhibition of keratinocyte hyperproliferation [13] activities. In particular, thiophene-containing compounds are of considerable interest as anticancer drugs [7–11].

Therefore, in recent years, extensive studies of the bioactivity of compounds containing the combination of thiophene and tetrazole cycles as selective inhibitors of histone deacetylase 6 [9] and CDK8 kinase [8]. This allows it to be considered as highly effective potential anticancer agents, as well as AT2 receptor ligands [14], anti-inflammatory and antibacterial agents [5]. Therefore, it is still perspective to continue studying of synthesis and reactivity of the compounds containing the thiophene and tetrazole fragments combinations.

2. Results and discussion

We have previously developed a convenient approach to the synthesis of 2-functionalized 5-aryl-3-aminothiophenes, in particular for nitriles of 3-amino-5-arylthiophene-2-carboxylic acids **1a-f**, by bromoarylation of α-chloroacrylonitrile, and subsequent cyclization of obtained products with chloroacetonitrile and sodium hydrosulfide [15].

The presence of an amino group and a nitrile group in the nitriles of 3-amino-5-arylthiophene-2-carboxylic acids **1a-f** allows the subsequent modification of such compounds or their use as building blocks for the construction of thiophene-containing target substances. We were able to modify nitriles of 3-amino-5-arylthiophene-2-carboxylic acids into thiophenyltetrazole derivatives **2a-f** using the reaction of [3+2] cycloaddition of azide and nitrile groups. By the reaction of 3-amino-5-arylthiophene-2-carbonitriles with sodium azide in the presence of ammonium chloride in DMF, the 5-aryl-2-(*5H*-tetrazol-5-yl)thiophen-3-amines have been obtained. Ammonium azide, which is significantly better soluble in DMF and capable for generating of hydrogen azide, was generated *in situ* by the interaction of ammonium chloride with sodium azide. Ammonium azide formation facilitates the reaction proceeding. The reaction was carried out under heating of reaction mixture at a temperature of 130 °C in an inert atmosphere to prevent an oxidation of the aminothiophene fragment and resinification, which was observed when mixture was heating at the presence of air. The target products **2a-f** were isolated by diluting with water and acidifying of the mixture to pH = 4.



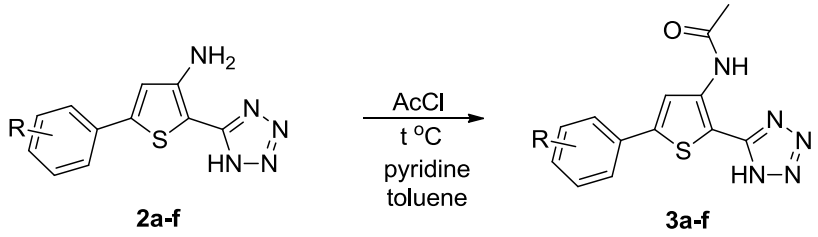
1a-f **2a-f**

R = H, 3-Me, 4-Me, 4-F, 3-CF_3, 4-CF_3

Thus, we obtained a number of new 2-(*1H*-tetrazol-5-yl)-5-aryl-3-aminothiophenes **2a-f** in yields of 70–92%. That way allows to the introduction of a large variety of functional groups in aryl substituent at the 5-position of the thiophene cycle. It can be expected that the tetrazole moiety of the obtained compounds serves as a convenient precursor for the construction of oxadiazoles. At the same time, the amino group presented in the 3 position of thiophene ring is suitable for the obtaining of different amides.

Thus, they can be used as bifunctional reagents for the forming of thiophene-containing polyheterocyclic compounds. Due to the prospects for the study of compounds such as antiproliferative agents, the anticancer activity of 5-aryl-2-(1H-tetrazol-5-yl)thiophen-3-amines is currently being studied.

However, it has been established that 2-tetrazolyl-3-aminothiophenes **2a-f** react with acethyl chloride forming N-(5-aryl-2-(*1H*-tetrazol-5-yl)thiophen-3-yl)acetamides **3a-f**.



2a-f **3a-f**

R= H, 3-Me, 4-Me, 4-F, 3-CF_3, 4-CF_3

Boiling the **2a-f** compounds with acetyl chloride in toluene at the presence of pyridine the acylation of amino group is performed without expected oxadiazole cycle forming.

3. Conclusion

In the current work, 2-(*1H*-tetrazol-5-yl)-5-aryl-3-aminothiophenes forming has been investigated. Moreover, present amino group in obtained tetrazolylaminothiophenes allows proceeding further modification, which makes possible to synthesize a range of N-(5-aryl-2-(*1H*-tetrazol-5-yl)thiophen-3-yl)acetamides with tetrazolyl substituent in thiophene ring easily.

4. Acknowledgements

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5. Experimental Section

Melting points are uncorrected and were determined in an apparatus according to Dr. Tottoli (Büchi). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR). Multiplicities are described by using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

General procedure for the synthesis of 5-aryl-2-(*1H*-tetrazol-5-yl) thiophen-3-amines 2a-f

3 Mmol of 3-amino-5-arylthiophene-2-carbonitrile, 0.390 g (6 mmol) of sodium azide, 0.321 g (6 mmol) of ammonium chloride and 4 ml of dry dimethylformamide were added to a Schlenk tube (25 ml). The Schlenk tube was evacuated three times and filled with dry argon. The reaction mixture was heated on a silicone bath with vigorous stirring at 130 °C (bath temperature) for 4 hours. The mixture was cooled and poured into 30 ml of ice water and acidified to pH = 4. The resulting precipitate was filtered off and recrystallized from ethanol.

5-Phenyl-2-(*1H*-tetrazol-5-yl)thiophen-3-amine (2a): Yield 0.517 g, 70 %, off-white crystals, m.p. 148–149 °C ^{1}H NMR (400 MHz, DMSO-d6), δ: 7.62 (d, 2H, C_6H_5), 7.45–7.41 (m, 2H, C_6H_5), 7.38–7.33 (m, 1H, C_6H_5), 7.10 (s, 1H, thiophene), 6.43 (s, 2H, NH_2). ^{13}C NMR (101 MHz, DMSO-d6), δ: 150.84, 145.26, 133.25, 129.71, 129.16, 125.72, 117.56. LC-MS (EI): *m/z* = 244.1 $[M+H]^+$. Elemental analysis calcd. for $C_{11}H_9N_5S$: C 54.31, H 3.73, N 28.79, found: C, 54.22; H, 3.62; N, 28.68.

2-(*1H*-Tetrazol-5-yl)-5-(m-tolyl)thiophen-3-amine (2b): Yield 0.578 g, 75 %, off-white crystals, m.p. 130–131 °C ^{1}H NMR (400 MHz, DMSO-d6), δ: 7.45–7.36 (m, 2H, C_6H_4), 7.32 (t, *J* = 7.4 Hz, 1H, C_6H_4), 7.17 (d, *J* = 7.0 Hz, 1H, C_6H_4), 7.04 (s, 1H, thiophene), 6.41 (s, 2H, NH_2), 2.35 (s, 3H, CH_3). LC-MS (EI): *m/z* = 258.1 $[M+H]^+$. Elemental analysis calcd. for $C_{12}H_{11}N_5S$: C 56.01, H 4.31, N 27.22, found: C, 55.88; H, 4.20; N, 27.09.

2-(*1H*-Tetrazol-5-yl)-5-(p-tolyl)thiophen-3-amine (2c): Yield 0.610 g, 79 %, off-white crystals, m.p. 153–154 °C ^{1}H NMR (400 MHz, DMSO-d6), δ: 7.45 (d, *J* = 8.2 Hz, 2H, C_6H_4), 7.27 (d, *J* = 8.1 Hz, 2H, C_6H_4), 6.87 (s, 1H, thiophene), 6.43 (s, 2H, NH_2), 2.32 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d6), δ: 150.74, 145.49, 138.82, 130.52, 130.22, 125.62, 117.01, 21.22. LC-MS (EI): *m/z* = 258.1 $[M+H]^+$. Elemental analysis calcd. for $C_{12}H_{11}N_5S$: C 56.01, H 4.31, N 27.22, found: C, 55.85; H, 4.22; N, 27.03.

5-(4-Fluorophenyl)-2-(*1H*-tetrazol-5-yl)thiophen-3-amine (2d): Yield 0.634 g, 81 %, off-white crystals, m.p. 137–138 °C ^{1}H NMR (400 MHz, DMSO-d6), δ: 10.35 (s, 1H), 7.64 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.24 (t, *J* = 8.8 Hz, 2H), 7.05 (s, 1H), 6.49 (br.s, 2H, NH_2). LC-MS (EI): *m/z* = 262.0 $[M+H]^+$. Elemental analysis calcd. for $C_{11}H_8FN_5S$: C 50.57, H 3.09, N 26.80, found: C, 50.41; H, 2.90; N, 26.66.

2-(*1H*-Tetrazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiophen-3-amine (2e): Yield 0.765 g, 82 %, off-white crystals, m.p. 140–141 °C. ^{1}H NMR (400 MHz, DMSO-d6), δ: 7.90–7.80 (m, 2H, C_6H_4), 7.80–7.70 (m, 1H, C_6H_4), 7.68–7.60 (m, 1H, C_6H_4), 7.13 (s, 1H, thiophene), 6.61 (s, 2H, NH_2). LC-MS (EI): *m/z* = 312.1 $[M+H]^+$. Elemental analysis calcd. for $C_{12}H_8F_3N_5S$: C 46.30, H 2.59, N 22.50, found: C, 46.13; H, 2.43; N, 22.38.

2-(*1H*-Tetrazol-5-yl)-5-(4-(trifluoromethyl)phenyl)thiophen-3-amine (2f): Yield 0.858 g, 92 %, off-white crystals, m.p. 162–163 °C. ^{1}H NMR (400 MHz, DMSO-d6), δ: 10.4 (s, 1H, NH), 7.72 (d, *J* = 8.1 Hz, 2H, C_6H_4), 7.52 (d, *J* = 8.0 Hz, 2H, C_6H_4), 7.15 (s, 1H, thiophene). LC-MS (EI): *m/z* = 312.1 $[M+H]^+$. Elemental analysis calcd. for $C_{12}H_8F_3N_5S$: C 46.30, H 2.59, N 22.50, found: C, 46.20; H, 2.44; N, 22.54.

General procedure for the synthesis of N-(5-aryl-2-(*1H*-tetrazol-5-yl)thiophen-3-yl)acetamides 3a-f

Mixture of 2 mmol of 2-(*1H*-tetrazol-5-yl)-5-aryl-3-aminothiophene, 0.43 ml (0.47 g, 6 mmol) of acetyl chloride, 0.49 ml (0.5 g, 6 mmol) of pyridine and 10 ml of dry toluene were refluxed with vigorous stirring for 4 hours. The mixture was cooled, toluene was evaporated under reduced pressure and diluted 30 ml of ice water. The resulting precipitate was filtered off and recrystallized from ethanol-DMF.

N-(5-phenyl-2-(*1H*-tetrazol-5-yl)thiophen-3-yl)acetamide (3a): Yield 0.479 g, 84 %, off-white crystals, m.p. 201–203 °C. ^{1}H NMR (400 MHz, DMSO-d6), δ: 10.08 (s, 1H, NH), 7.98 (s, 1H, thiophene), 7.52–7.43 (m, 5H, C_6H_5), 2.29 (s, 3H, CH_3). LC-MS (EI): *m/z* = 286.1 $[M+H]^+$. Elemental analysis calcd. for $C_{13}H_{11}N_5OS$: C 54.72, H 3.89, N 24.55, found: C, 54.60; H, 3.78; N, 24.48.

N-(2-(*1H*-tetrazol-5-yl)-5-(m-tolyl)thiophen-3-yl)acetamide (3b): Yield 0.437 g, 73 %, off-white crystals, m.p. 190–191 °C. ^{1}H NMR (400 MHz, DMSO-d6), δ: 10.00 (s,

1H, NH), 7.88 (s, 1H, thiophene), 7.54–7.50 (m, 1H, C_6H_4), 7.45 (s, 1H, C_6H_4), 7.28-7.20 (m, 2H, C_6H_4), 2.30 (s, 3H, CH_3), 2.17 (s, 3H, CH_3). LC-MS (EI): *m/z* = 300.1 $[M+H]^+$. Elemental analysis calcd. for $C_{14}H_{13}N_5OS$: C 56.17, H 4.38, N 23.40, found: C, 56.03; H, 4.31; N, 23.43.

N-(2-(*1H*-tetrazol-5-yl)-5-(p-tolyl)thiophen-3-yl)acetamide (3c): Yield 0.484 g, 81 %, off-white crystals, m.p. 205–206 °C. ^{1}H NMR (400 MHz, DMSO-d6), δ: 10.08 (s, 1H, NH), 7.98 (s, 1H, thiophene), 7.53 (d, *J* = 8.1, 2H, C_6H_4), 7.24 (d, *J* = 8.0, 2H, C_6H_4), 2.30 (s, 3H, CH_3), 2.14 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d6), δ: 167.9, 145.0, 138.7, 138.6, 129.9, 129.7, 125.3, 119.3, 106.4, 23.9, 20.8. LC-MS (EI): *m/z* = 300.1 $[M+H]^+$. Elemental analysis calcd. for $C_{14}H_{13}N_5OS$: C 56.17, H 4.38, N 23.40, found: C, 56.07; H, 4.28; N, 23.30.

N-(5-(4-fluorophenyl)-2-(*1H*-tetrazol-5-yl)thiophen-3-yl)acetamide (3d): Yield 0.510 g, 84 %, off-white crystals, m.p. 197–198 °C. ^{1}H NMR (400 MHz, DMSO-d6), δ: 10.00 (s, 1H, NH), 7.96 (s, 1H, thiophene), 7.53 (dd, J_{HH} = 8.2, J_{HF} = 5.1, 2H, C_6H_4), 7.30 (t, *J* = 8.1, 2H, C_6H_4), 2.29 (s, 3H, CH_3). LC-MS (EI): *m/z* = 304.1 $[M+H]^+$. Elemental analysis calcd. for $C_{13}H_{10}FN_5OS$: C 51.48, H 3.32, N 23.09, found: C, 51.34; H, 3.22; N, 23.00.

N-(2-(*1H*-tetrazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiophen-3-yl)acetamide (3e): Yield 0.558 g, 79 %, off-white crystals, m.p. 211–212 °C. ^{1}H NMR (400 MHz, DMSO-d6), δ: 10.10 (s, 1H, NH), 7.98 (s, 1H, thiophene), 7.53–7.48 (m, 2H, C_6H_4), 7.30–7.22 (m, 2H, C_6H_4), 2.28 (s, 3H, CH_3). LC-MS (EI): *m/z* = 354.1 $[M+H]^+$. Elemental analysis calcd. for $C_{14}H_{10}F_3N_5OS$: C 47.59, H 2.85, N 19.82, found: C, 47.44; H, 2.73; N, 19.79.

N-(2-(*1H*-tetrazol-5-yl)-5-(4-(trifluoromethyl)phenyl)thiophen-3-yl)acetamide (3e): Yield 0.622 g, 88 %, off-white crystals, m.p. 223–224 °C. ^{1}H NMR (400 MHz, DMSO-d6), δ: 10.00 (s, 1H, NH), 7.95 (s, 1H, thiophene), 7.58 (d, *J* = 8.5, 2H, C_6H_4), 7.30 (d, *J* = 8.4, 2H, C_6H_4), 2.30 (s, 3H, CH_3). LC-MS (EI): *m/z* = 354.1 $[M+H]^+$. Elemental analysis calcd. for $C_{14}H_{10}F_3N_5OS$: C 47.59, H 2.85, N 19.82, found: C, 47.48; H, 2.71; N, 19.77.

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СИНТЕЗ ЗАМІЩЕНИХ 5-(ТІОФЕН-2-ІЛ)-1Н-ТЕТРАЗОЛІВ

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Описано метод отримання тетразоліламінотіофенів взаємодією 3-аміно-5-арилтіофен-2-карбонітрилів з азидом амонію в середовищі ДМФА з високими виходами. Таким способом одержано нові, раніше не описані, функціоналізовані похідні 3-амінотіофену з високими виходами та чистотою: 5-феніл-2-(*1H*-тетразол-5-іл)тіофен-3-амін, 2-(*1H*-тетразол-5-іл)-5-(*м*-толіл)тіофен-3-амін, 2-(*1H*-тетразол-5-іл)-5-(*п*-толіл) тіофен-3-амін, 5-(4-флуорофеніл)-2-(*1H*-тетразол-5-іл)тіофен-3-амін, 5-(3-трифлуорометилфеніл)-2-(*1H*-тетразол-5-іл)тіофен-3-амін, 5-(4-трифлуорометилфеніл)-2-(*1H*-тетразол-5-іл)тіофен-3-амін. Показано можливість введення різноманітних арильних замісників у п'ятому положенні тіофенового циклу, які визначаються використаним вихідним аніліном. Наявність в отриманих тетразоліламінотіофенах аміногрупи та тетразольного кільця робить їх перспективними будівельними блоками, придатними для побудови різних тіофенвмісних гетероциклічних систем.

Показано можливість селективного отримання N-(5-арил-2-(*1H*-тетразо-5-іл)тіофен-3-іл)ацетамідів ацилюванням 2-(*1H*-тетразол-5-іл)-5-арил-3-амінотіофенів, дією ацетил хлориду за наявності піридину, як основи, в середовищі толуену за температури кипіння. З'ясовано, що рециклізація тетразольного фрагмента до оксадіазольного циклу в умовах реакції не відбулася, а простежувалося лише ацилювання аміногрупи.

Одержані сполуки містять тіофеновий та тетразольний фармакофорні фрагменти та є перспективними для вивчення біологічної активності. Вони пройшли відбір для дослідження на протиракову активність у рамках співпраці з Національним інститутом раку (США).

Ключові слова: тетразоліл-3-амінотіофени, [3+2] циклоприєднання, ацилювання, 3-аміно-5-арил-2-ціанотіофени.

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