ISSN 2078-5615. Вісник Львівського університету. Серія хімічна. 2021. Випуск 62. С. 183–190
Visnyk of the Lviv University. Series Chemistry. 2021. Issue 62. P. 183–190

Органічна хімія

УДК 547.732.7+ 547.793.4

SYNTHESIS OF NOVEL 3-(1,2,4-OXADIAZOL-5-YL)THIOPHEN-2-AMINE DERIVATIVES VIA GEWALD REACTION

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Novel substituted 3-(1,2,4-oxadiazol-5-yl)thiophen-2-amines were obtained by the multicomponent Gewald reaction of an activated nitrile with 1,2,4-oxadiazole moiety, a carbonyl component and elemental sulphur in the presence of morpholine as a catalyst.

Keywords: 2-aminothiophenes, 1,2,4-oxadiazole, Gewald reaction, multicomponent reaction.

DOI: https:/doi.org/10.30970/vch.6201.183

1. Introduction

Gewald multicomponent reaction has received much attention because of its elegance, versatility, convenience, and effectiveness [1, 2]. A number of methods for the synthesis of 2-aminothiophene derivatives has been developed using such strategy and a wide range of functionalized 2-aminothiophenes has been prepared [1–4]. Moreover, produced by Gewald reaction 2-aminothiophenes are important five-membered heterocyclic building blocks in organic synthesis, and the chemistry of these small molecules is still developing [3]. Thiophene derivatives are utilized in industrial chemistry and material science as corrosion inhibitors, organic semiconductors, organic field-effect transistors (OFETs) [5], organic light-emitting diodes (OLEDs) [6], etc. Still special attention is given to biologically and pharmacologically attractive aminothiophene derivatives. Till now, 2-aminothiophene scaffold prove to act as efficient synthon for the synthesis of biological active thiophene-containing heterocycles [3, 7].

From the other point of view, 1,3,4-oxadiazoles and 1,2,4-oxadiazoles derivatives are widely investigated and represent another important scaffold for current drug discovery due to the remarkable biological properties possessed by oxadiazole derivatives [8, 9]. The oxadiazole scaffold is found in a series of compounds with anticonvulsant, anti-inflammatory, antiallergic, antipsychotic, antimicrobial, antitumor, antiviral and anti-tuberculosis activity [10]. Some of them also act as antidepressants and analgesics. Therefore, both the development of the synthesis of new oxadiazole derivatives and evaluation of their biological activity are in high demand.

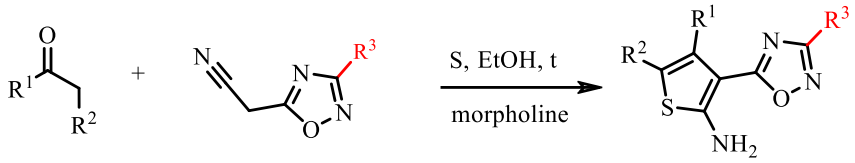
Our previous studies on aminothiophenes established some convenient chemical modifications of the Gewald 2-aminothiophenes and isomeric 3-aminothiophenes, the scope of their synthetic application in various fused nitrogen containing heterocycles preparation

in energy-saving and environmentally friendly manner was also determined [11–19]. Such approaches allowed to create broad combinatorial libraries for drug discovery and to select drug-like examples possessing significant anticancer activity [20–22].

Thus, synthesis of novel functionalized 3-(1,2,4-oxadiazol-5-yl)thiophen-2-amines will broaden the combinatorial library with the aim of the anticancer agent search.

2. Results and discussion

Herein, based on multicomponent Gewald method [23] a number of new 3-(5-aryl-1,3,4-oxadiazol-2-yl)thiophen-2-amines **3a-j** were obtained with high yield. Proposed protocol involves multicomponent condensation of an activated nitrile, a carbonyl component and elemental sulphur in the presence of morpholine as a catalyst. The facility of one-pot multicomponent Gewald rection also allows to implement the variety of carbonyl components as well as nitriles with substituents of different nature.



1a,b **2a-e** **3a-j**

1: R^1=R^2= Me (**b**), R^1+R^2 = -$(CH_2)_4$- (**a**)

2: R^3 = Ph (**a**), 2-MeC_6H_4 (**b**), 4-FC_6H_4 (**c**), 2-ClC_6H_4 (**d**), 4-ClC_6H_4 (**e**)

Gewald reaction of carbonyl compoumds **1a, b** with (1,2,4-oxadiazol-5-yl)acetonitriles **2a-e**
Реакція Гевальда карбонільних сполук **1a, b** з (1,2,4-оксадіазол-5-іл)ацетонітрилами **2a-e**

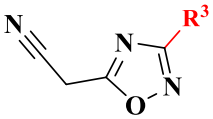
To determine the possibility of successful implementation of new heterocyclic nitriles with oxadiazole ring **2a–d** in such synthetic protocol we performed experiments with well-established model carbonyl components such as ethyl 3-oxobutanoate **1a** and cyclohexanone **1**. On contrary, mentioned starting (1,2,4-oxadiazol-5-yl) acetonitriles **2a-e** (*Table 1*) were studied in Gewald protocol for the first time to determine if 1,2,4-oxadiazole ring is a good acceptor suitable for Knoevenagel condensation and does the proposed conditions tolerates 1,2,4-oxadiazol moiety at all. (1,2,4-Oxadiazol-5-yl)acetonitriles with both donor and acceptor substituents were recently described by our group and the scope of their application in green click protocols with azides was established [24]. The experiment showed that these conversations were performed in good yields.

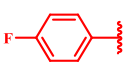
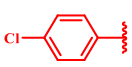
Table 1

Nitriles **2a-e**

Таблиця 1

Нітрили **2a-e**



ID	2a	2b	2c	2d	2e
R^3					

We found out that reaction proceeds smoothly and desired functionalized aminothiophenes with additional heterocyclic ring –1,2,4-oxadiazole **3a-j** were obtained as crystalline compounds of high purity and with good yields (*Table 2*). The structure of isolated products was confirmed by ^{1}H and ^{13}C NMR spectroscopy. Utilization of (1,2,4-oxadiazol-5-yl)acetonitriles and ketones allowed to form a series of previously undescribed aminothiophenes, suitable for biological screening or further modification.

It should be mentioned, that the utility of easily accessible nitriles with 1,2,4-oxadiazole allows to vary the substituent in aryl core, what would broaden combinatorial library of biologically suitable 1,2,4-oxadiazolyl-thiophene derivatives.

Moreover, the synthesized 3-(aryl)-1,2,4-oxadiazol-5-yl)-thiophen-2-amines **3a-j** were submitted and selected by NCI (National Cancer Institute, USA) for evaluation at the single concentration towards a panel of the approximately sixty cancer cell lines among nine different cancer types: leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancers (http://dtp.nci.nih.gov).

The obtained compounds were also selected by Community for Open Antimicrobial Drug Discovery (CO-ADD) (UK, Australia) to test antimicrobial properties. The results of biological experiments will be reported in a due course.

3. Conclusion

In the current work, we investigated the one-pot multicomponent Gewald protocol, which made possible to easily synthesize a range of functionalized 1,2,4-oxadiazolyl aminothiophene compounds suitable for screening on biological activity in cost and time effective manner from available reagents and ability to vary substituents. The products – 3-(aryl)-1,2,4-oxadiazol-5-yl)-thiophen-2-amines were obtained for the first time in good yields and high purity. Moreover, present amino group in obtained Gewald thiophenes allows further modification on demand to improve pharmacologic profile of substances.

4. Experimental part

^{1}H and ^{13}C NMR spectra were recorded on Varian Unity Plus 400 (400 and 101 MHz, respectively), Bruker 170 Avance 500 (500 and 126 MHz, respectively) spectrometers in DMSO-d_6 solutions using TMS or the deuterated solvent as internal reference. Elemental analyses were accomplished using a Carlo Erba 1106 instrument. Melting points were determined on a Boetius melting point apparatus.

General Procedure for the synthesis of 2-aminothiophenes 3a-j

Elemental sulphur (0,01 mol) and morpholine (0,8 ml) was added to a solution of carbonyl component **1a**,**b** (0,01mol) and activated with oxadiazole ring nitrile **2a-e** (0,01mol) in EtOH. The mixture was stirred and heated to 50–60°C at reflux for 3 h. The reaction mixture was cooled to the room temperature and the formed solid was filtered off and recrystallized from ethanol.

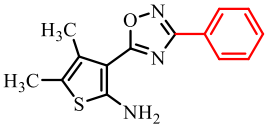
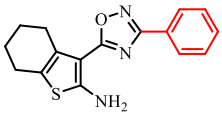
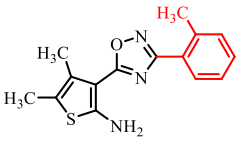
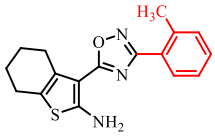
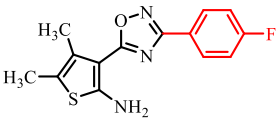
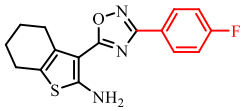
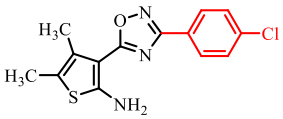
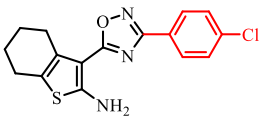
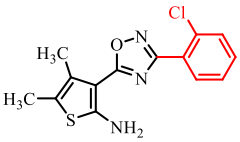
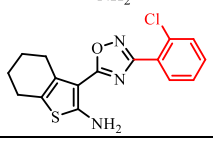
4,5-Dimethyl-3-(3-phenyl-1,2,4-oxadiazol-5-yl)thiophen-2-amine 3a. Yield 81 %. M.p. = 164–165 °C. ^{1}H NMR (400 MHz, DMSO-d_6) ppm: δ 2,15 (s, 3H, Me), 2,25 (s, 3H, Me), 7,53–7,75 (m, 3H, H_{Ph}-3,4,5), 7,80 (br. s, 2H, NH_2), 8,10–8,16 (m, 2H, H_{Ph}-2,6).^{13}C NMR (101 MHz, DMSO-d_6) ppm: δ 173,40 (C_{Oxadz}-5), 166,58 (C_{Oxadz}-3), 160,31(C_{Th}), 131,70(C_{Th}), 129,51 (2xC_{Ph}-3,5), 128,04 (C_{Ph}-4), 127,68 (2xC_{Ph}-2,6), 127,13 (C_{Ph}-1), 114,52 (C_{Th}), 99,02 (C_{Th}), 14,42 (Me), 12,44 (Me). Found, %: C 61,94; H 4,85; N 15,53.$C_{14}H_{13}N_3OS$. Calculated, C 61,97; H 4,83; N 15,49.

Table 2

Yields and melting point of synthesized compounds **3a-j**

Таблиця 2

Виходи і температури плавлення синтезованих сполук **3a-j**

ID	Structure	Yield, %	mp, °C
3a		81	164–165
3b		82	200–201
3c		68	179–180
3d		72	185–186
3e		75	203–204
3f		78	194–195
3g		74	216–217
3h		73	188–189
3i		69	166–167
3j		71	183–184

3-(3-Phenyl-1,2,4-oxadiazol-5-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-amine 3b. Yield 82 %. M.p. = 200–201 °C. ^{1}HNMR (400 MHz, DMSO-d_6) ppm: δ 1,73 (br. s, 4H, CH_2), 2,45 (br. s, 2H, CH_2), 2,73 (br. s, 2H, CH_2), 7,51–7,55 (m, 3H, H_{Ph}-3,4,5), 7,68 (br. s, 2H, NH_2), 8,09–8,11 (m, 2H, H_{Ph}-2,6).^{13}C NMR (101 MHz, DMSO-d_6) ppm: δ 173,31 (C_{Oxadz}-5), 166,58 (C_{Oxadz}-3), 160,86 (C_{Th}), 131,60 (C_{Th}), 130,40 (C_{Ph}-4), 129,43 (2xC_{Ph}-3,5), 127,64 (2xC_{Ph}-2,6), 127,17 (C_{Ph}-1), 117,87 (C_{Th}), 97,74 (C_{Th}), 26,17 (CH_2), 24,29 (CH_2), 23,20 (CH_2), 22,67 (CH_2). Found, %: C 64,57; H 5,10; N 14,16.$C_{16}H_{15}N_3OS$. Calculated, C 64,62; H 5,08; N 14,13.

4,5-Dimethyl-3-(3-(o-tolyl)-1,2,4-oxadiazol-5-yl)thiophen-2-amine 3c. Yield 68 %. M.p. = 179–180 °C. ^{1}HNMR (400 MHz, DMSO-d_6) ppm: δ 2,14 (s, 3H, CH_3), 2,25 (s,3H, CH_3), 2,57 (s,3H, CH_3), 7,33–7,37 (m, 2H, H_{Ar}-3,5), 7,41–7,44 (m, 1H, H_{Ar}-4), 7,59 (br. s, 2H, NH_2), 8,03 (d, 1H, J = 7,6 Hz, H_{Ar}-6).^{13}C NMR (101 MHz, DMSO-d_6) ppm: δ 172,42 (C_{Oxadz}-5), 167,21 (C_{Oxadz}-3), 160,07(C_{Th}), 137,90(C_{Th}), 131,76 (C_{Ar}), 130,96 (C_{Ar}), 130,34 (C_{Ar}), 128,11 (C_{Ar}), 126,57 (C_{Ar}), 126,46 (C_{Ar}), 114,55 (C_{Th}), 99,11 (C_{Th}), 24,27 (CH_3), 14,39 (CH_3), 12,41 (CH_3). Found, %: C 63,17; H 5,28; N 14,76. $C_{15}H_{15}N_3OS$. Calculated, C 63,13; H 5,30; N 14,73.

3-(3-(o-Tolyl)-1,2,4-oxadiazol-5-yl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-amine 3d. Yield 72 %. M.p. = 185–186 °C. ^{1}HNMR (400 MHz, DMSO-d_6) ppm: δ 1,72 (br. s, 4H, CH_2), 2,46 (br. s, 2H, CH_2), 2,56 (s,3H, CH_3), 2,71 (br. s, 2H, CH_2), 7,34–7,37 (m, 2H, H_{Ar}-3,5), 7,40–7,43 (m, 1H, H_{Ar}-4), 7,57 (br. s, 2H, NH_2), 8,03 (d, 1H, J = 7,6 Hz, H_{Ar}-6). Found, %:C 65,61; H 5,48; N 13,51. $C_{17}H_{17}N_3OS$. Calculated, C 65,57; H 5,50; N 13,49.

3-(3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-amine 3e. Yield 75 %. M.p. = 203–204 °C. ^{1}HNMR (500 MHz, DMSO-d_6) ppm: δ 2,13 (s, 3H, CH_3), 2,23 (s,3H, CH_3), 7,38–7,33 (m, 2H, H_{Ar}-3,5), 7,66 (br. s, 2H, NH_2), 8,16-8,24 (m, 2H, H_{Ar}-2,6).^{13}C NMR (126 MHz, DMSO-d_6) ppm: δ 173,42 (C_{Oxadz}-5), 165,76 (C_{Oxadz}-3), 163,04 (C_{Th}), 160,40 (d, $^1J_{C\text{-}F}$ = 249,4 Hz, C_{Ar}-4), 130,16 (d, $^3J_{C\text{-}F}$ = 8,8 Hz, 2xC_{Ar}-2,6), 128,00(C_{Th}), 123,70 (d, ^4J = 2,8 Hz, C_{Ar}-1), 116,55 (d, $^2J_{C\text{-}F}$ = 22,0 Hz, 2xC_{Ar}-3,5), 114,48 (C_{Th}), 98,94 (C_{Th}), 14,38 (CH_3), 14,40 (CH_3). Found, %: C 58,16; H 4,20; N 14,45. $C_{14}H_{12}FN_3OS$. Calculated, C 58,12; H 4,18; N 14,52.

3-(3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-amine 3f. Yield 78 %. M.p. = 194–195 °C. ^{1}HNMR (500 MHz, DMSO-d_6) ppm: δ 1,73 (br. s, 4H, CH_2), 2,46 (br. s, 2H, CH_2), 2,72 (br. s, 2H, CH_2), 7,35 (t, J = 8,6 Hz, 2H, H_{Ar}-3,5), 7,67 (br. s, 2H, NH_2), 8,15 (dd, J = 8,6, 5,4 Hz, 2H, H_{Ar}-2,6). ^{13}C NMR (126 MHz, DMSO-d_6) ppm: δ 173,33 (C_{Oxadz}-5), 165,80 (C_{Oxadz}-3), 163,03 (C_{Th}), 160,97 (d, $^1J_{C\text{-}F}$ = 249,4 Hz, C_{Ar}-4), 130,37 (C_{Th}), 130.15 (d, $^3J_{C\text{-}F}$ = 8,9 Hz, 2xC_{Ar}-2,6), 123.70 (d, ^4J = 2,8 Hz, C_{Ar}-1), 117,85 (C_{Th}), 116.56 (d, $^2J_{C\text{-}F}$ = 22,0 Hz, 2xC_{Ar}-3,5), 97,60 (C_{Th}), 26,15 (CH_2), 24,28 (CH_2), 23,19 (CH_2), 22,66 (CH_2). Found, %:C 60,99; H 4,46; N 13,29. $C_{16}H_{14}FN_3OS$. Calculated, C 60,94; H 4,47; N 13,32.

3-(3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-amine 3g. Yield 74 %. M.p. = 216–217 °C. ^{1}HNMR (400 MHz, DMSO-d_6) ppm: δ 2,14 (s, 3H, CH_3), 2,24 (s,3H, CH_3), 7,60 (d, 2H, J = 8,3 Hz, H_{Ar}-3,5), 7,67 (br. s, 2H, NH_2), 8,13 (d, 2H, J = 8,3, H_{Ar}-2,6). ^{13}C NMR (101 MHz, DMSO-d_6) ppm: δ 173,51 (C_{Oxadz}-5), 165,80 (C_{Oxadz}-3), 160,52 (C_{Th}), 136,42 (C_{Th}), 129,63 (2xC_{Ar}-3,5), 129,48 (2xC_{Ar}-2,6), 127,99 (C_{Ar}-4), 125,99 (C_{Ar}-1), 114,53 (C_{Th}), 99,88 (C_{Th}), 14,40 (CH_3), 12,44 (CH_3). Found, %: C 54,92; H 3,98; N 13,77. $C_{14}H_{12}ClN_3OS$. Calculated, C 54,99; H 3,96; N 13,74.

3-(3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-amine 3h. Yield 73 %. M.p. = 188–189 °C. ^{1}HNMR (400 MHz, DMSO-d_6) ppm: δ 1,74 (br. s,

4H, CH_2), 2,47 (br. s, 2H, CH_2), 2,72 (br. s, 2H, CH_2), 7,62–7,64 (m, 3H, H_{Ar}-3,4,5), 7,68 (br. s, 2H, NH_2), 8,12 (d, *J* = 8,6 Hz, 2H, H_{Ar}-2,6). ^{13}C NMR (101 MHz, DMSO-d_6) ppm: δ 173,41 (C_{Oxadz}-5), 165,82 (C_{Oxadz}-3), 161,08 (C_{Th}), 136,38 (C_{Th}), 130,35 (C_{Ar}-4), 129,58 (2xC_{Ar}-3,5), 129,45 (2xC_{Ar}-2,6), 126,01 (C_{Ar}-1), 117,90 (C_{Th}), 97,55 (C_{Th}), 26,15 (CH_2), 24,29 (CH_2), 23,18 (CH_2), 22,65 (CH_2). Found, %: C 57,98; H 4,28; N 12,57. $C_{16}H_{14}ClN_3OS$. Calculated, C 57,92; H 4,25; N 12,66.

3-(3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-amine 3i. Yield 69 %. M.p. = 166–167 °C. ^{1}HNMR (400 MHz, DMSO-d_6) ppm: δ 2,14 (s, 3H, CH_3), 2.26 (s,3H, CH_3), 7,50–7,61 (m, 5H, H_{Ar}-3,4,5+NH_2), 8,03 (m, 1H, H_{Ar}-6).^{13}C NMR (101 MHz, DMSO-d_6) ppm: δ 172,84 (C_{Oxadz}-5), 165,47 (C_{Oxadz}-3), 160,42 (C_{Th}), 132,67 (C_{Th}), 132,31 (C_{Ar}), 131,23 (2xC_{Ar}), 128,00 (2xC_{Ar}), 126,36 (C_{Ar}), 114,67 (C_{Th}), 98,91 (C_{Th}), 14,38 (CH_3), 12,43 (CH_3). Found, %: C 54,91; H 3,99; N 13,76. $C_{14}H_{12}ClN_3OS$. Calculated, C 54,99; H 3,96; N 13,74.

3-(3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-amine 3j. Yield 71 %. M.p. = 183–184 °C. ^{1}HNMR (400 MHz, DMSO-d_6) ppm: δ 1,73 (br. s, 4H, CH_2), 2,47 (br. s, 2H, CH_2), 2,74 (br. s, 2H, CH_2), 7,48–7,56 (m, 3H, H_{Ar}-3,4,5), 7,63 (br. s, 2H, NH_2), 8,03 (d, *J* = 7,6 Hz, 2H, H_{Ar}-2,6).^{13}C NMR (101 MHz, DMSO-d_6) ppm: δ 172,76 (C_{Oxadz}-5), 165,52 (C_{Oxadz}-3), 160,09 (C_{Th}), 132,63 (2xC_{Ar}), 132,29 (C_{Ar}), 131,20 (C_{Ar}), 130,36 (C_{Th}), 127,97 (C_{Ar}), 126,39 (C_{Ar}), 118,05 (C_{Th}), 97,59 (C_{Th}), 26,15 (CH_2), 24,29 (CH_2), 23,21 (CH_2), 22,67 (CH_2). Found, %: C 57,82; H 4,31; N 12,71. $C_{16}H_{14}ClN_3OS$. Calculated, C 57,92; H 4,25; N 12,66.

This work was supported by the National Research Foundation of Ukraine (Project No. 2020.01/0166) and the Ministry of Education and Science of Ukraine (Grant No. 0121U107777).

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СИНТЕЗ НОВИХ ПОХІДНИХ 3-(1,2,4-ОКСАДІАЗОЛ-5-ІЛ)-2-АМІНОТІОФЕНІВ РЕАКЦІЄЮ ҐЕВАЛЬДА

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Для синтезу нових заміщених 3-(1,2,4-оксадіазол-5-іл)-2-амінотіофенів використано однореакторну мультикомпонентну реакцію Ґевальда. Цей синтетичний протокол передбачає взаємодію нових реактантів – (3-арил-[1,2,4]оксадіазол-5-іл)ацетонітрилів з метиленактивними карбонільними сполуками (циклогексанон, етилметилкетон) і сіркою за наявності морфоліну як каталізатора. Таким способом одержано нові, раніше не описані, функціоналізовані похідні 3-(1,2,4-оксадіазол-5-іл)-2-амінотіофени з високими виходами та чистотою: 4,5-диметил-3-(3-феніл-1,2,4-оксадіазол-5-іл) тіофен-2-амін, 3-(3-феніл-1,2,4-оксадіазол-5-іл)-4,5,6,7-тетрагідробензо[*b*]тіофен-2-амін, 4,5-диметил-3-(3-(*o*-толіл)-1,2,4-оксадіазол-5-іл)тіофен-2-амін, 3-(3-(*o*-толіл)-1,2,4-оксадіазол-5-іл)-4,5,6,7-тетрагідробензо[*b*]тіофен-2-амін, 3-(3-(4-фторофеніл)-1,2,4-оксадіазол-5-іл)-4,5-диметилтіофен-2-амін, 3-(3-(4-фторофеніл)-1,2,4-оксадіазол-5-іл)-4,5,6,7-тетрагідробензо-[*b*]тіофен-2-амін, 3-(3-(4-хлорофеніл)-1,2,4-оксадіазол-5-іл)-4,5-диметилтіофен-2-амін, 3-(3-(4-хлорофеніл)-1,2,4-оксадіазол-5-іл)-4,5,6,7-тетрагідробензо[*b*]тіофен-2-амін, 3-(3-(2-хлорофеніл)-1,2,4-оксадіазол-5-іл)-4,5-диметилтіофен-2-амін, 3-(3-(2-хлорофеніл)-1,2,4-оксадіазол-5-іл)-4,5,6,7-тетрагідробензо[*b*]тіофен-2-амін. Показано можливість успішного варіювання замісників у ацетонітрилах, що є перевагою для створення комбінаторних бібліотек амінотіофенового скафолду з 1,2,4-оксадіазольним фрагментом з метою пошуку лікарських препаратів. Будову цільових амінотіофенів підтверджено методами ^{1}H та ^{13}C ЯМР-спектроскопії.

Одержані сполуки є перспективними для вивчення біологічної активності. Вони пройшли відбір для дослідження протиракової активності у рамках співпраці з Національним інститутом раку (США), а антимікробної активності – зі Спільнотою з відкриття протимікробних препаратів (CO–ADD) (Велика Британія, Австралія).

Ключові слова: 1,2,4-оксадіазол, 2-амінотіофени, реакція Ґевальда, мультикомпонентні реакції.

Стаття надійшла до редколегії 01.11.2020
Прийнята до друку 18.05.2021