Ring closing metathesis strategies to isoxazole containing thiadiazepines

Olexandr V. Pavliuk*, Yuriy V. Bezugly, Volodimir I. Kashkovsky

V. P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Science of Ukraine, Murmaska Street, 94, Kyiv 02660, Ukraine

pavluiksasha@gmail.com

Keywords: *sulfamides, isoxazole, thiadiazepine, diallyl derivatives, ring closing metathesis.*

Cyclic sulfamides are attractive molecules with potential application in medical chemistry. It is known that thiadiazepine-containing derivatives demonstrate promising value in the development of protease inhibitors such as HIV protease, serine protease and metaloprotease. We demonstrate here a comfortable synthetic sequence to symmetric thiadiazepines containing isoxazole substituents. The structure of the obtained substances was confirmed by ^1H , ^{13}C NMR spectroscopy.

Introduction

One of the most famous classes of synthetic bacteriostatic antibiotics that are widely used in medicine are sulfamides. A large number of substances of this type became well-known drugs such as streptocide [1], furacemide [2], amprenavir [3], E7070 [4], sulfatiazole [1], acetazolamide [5], and others. Recently, the ability of the sulfamide fragment to inhibit some classes of enzymes that affect various physiological processes has been discovered. This facilitated the development of drugs for the treatment of glaucoma [6], epilepsy [7], arthritis [8], osteoporosis [9], Alzheimer's disease [10], cancer [11], and others. Cyclic sulfamides are very important scaffolds both in medicinal chemistry and in synthetic organic chemistry [12], among of them, have been found substances that have proven themselves as

peptidomimetics, in particular, HIV-proteinase inhibitors [13], [14]. Thus, in particular, N, N'-disubstituted derivatives of thiodiazepines were active inhibitors of HIV-1 proteinase [15], [16]. A number of substances of this type have been patented as anti-HIV agents [17]. Taking into account the need for a constant search for new potentially biologically active substances and a variety of biological activity of the isoxazole

Derivative, [18], [19], [20], [21] we offered a way of obtaining new isoxazole-containing derivatives of thiodiazepines using as key stage of the synthesis ring closing metathesis reactions [22], [23].

Results and Discussion

One of the advantages of this strategy is the formation in the process of obtaining a cycles with double bonds, which if necessary could be used to introduce into the seven-

membered cycle of the necessary pharmacophore groups. Using this strategy, we have obtained several new symmetric isooxazole-containing thiadiazepines.

As starting compounds for achieving the stated goal, we have used, as described in

the literature (**2a-b**) [24], and as new 3-substituted-5-aminomethyl isoxazoles (**2 c-d**) [25], which have been synthesized from the previously described brominated derivatives (**1a-b**) [26], by the method of Delepine (**Scheme 1**).

Scheme 1. Synthesis 3-substituted-5-aminomethyl isoxazoles and corresponding sulfamides.

A series of new sulfamides (**3 a-d**) was synthesized by the interaction of amine hydrochlorides (**2 a-d**) with sulfonyl chloride in the presence of triethylamine. Acylation of amines with sulfonyl chloride was carried out in solutions of dichloromethane at a temperature of about 0 °C for 1.5-2 hours. Target products (**3 a-d**) were obtained with 66-76 % yields. The structure of obtained compounds is confirmed

by the data of chromatomas spectra, ¹H, ¹³C NMR spectra and elemental analysis.

Sulfonylamides (**3 a-d**) were alkylated on two amide nitrogen atoms with 2.2 equivalents of allyl bromide (10 % excess) in DMF solutions at a temperature of 64-75 °C in the presence of a 2.3 equivalents of potassium carbonate (15 % excess) (**Scheme 2**).

Scheme 2. Synthesis diallyl containing sulfamides and corresponding isoxasole containing derivatives of thiadiazepine.

Diallyl derivatives (**4a-d**) were isolated with 73-81% yields. Their structure is confirmed by chromatomass spectra, elemental analysis and data of ^1H , ^{13}C NMR spectra. Ring-closing metathesis reactions of the derivative (**4a-d**) were carried out in solutions of dry degassed dichloromethane in the atmosphere of dry argon at a temperature of 25-30 °C for 10-12 hours using a ruthenium-carbene catalyst ($[\text{Ru}]$) (**Scheme 2**). The products (**5a-d**) were isolated after chromatographic purification with 74-85 % yields. Their structure is confirmed by chromatomass spectra, elemental analysis and data of ^1H , ^{13}C NMR spectra, elemental analysis. The disappearance of the signals of four protons of terminal $=\text{CH}_2$ - groups in the region of 5.33 ppm and two allylic $-\text{CH}=\text{}$ groups in the 5.8 ppm that are present in the spectra of the starting compounds (**4a-d**), as well as the appearance of the specific signal at the 4.6 ppm indicates the formation of thiadiazepine ring. In the ^{13}C NMR spectra of each of the compounds

(**5a-d**), there is a signal of C atoms at 127.7 ppm, characteristic of the sp^2 hybridized carbon atoms of the seven-membered ring, and there is no signal of the carbon atoms of the terminal $=\text{CH}_2$ -groups at 120.7 ppm, observed in the spectra of the starting diallyl derivatives (**4a-d**).

Experimental part

General information: ^1H NMR (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on Bruker Avance DRX 500 spectrometer in CDCl_3 , DMSO- d_6 solution with TMS. Chromatomass spectra were recorded using a liquid chromatography-mass spectrometric system using an Agilent 1100 Series high performance liquid chromatograph equipped with a diode array with an Agilent LC/MSD SL mass-selective detector (ionization method - is the chemical ionization at atmospheric pressure, APCI). Parameters of chromatography-mass analysis: column-Zorbax SB-C18, 1.8 μm , 4.6 x 15 mm; solvents A)

MeCN-H₂O 95: 5, 0,1% aqueous CF₃COOH, B) 0,1% aqueous CF₃COOH; flow eluent – 3 ml / min; Injection volume – 1 µm; UV detectors- 215, 254, 285 nm; Cl at atmospheric pressure. Elemental analysis was carried out in the laboratory of analytical chemistry of the Institute of Bioorganic Chemistry and Petrochemistry of the National Academy of Sciences of Ukraine: the carbon and hydrogen content was determined by the weight method of Pregle, nitrogen by the Dumas gas meterind method, and chlorine by the mercuric method. For column chromatography, was used silica gel Merck Grade 9385, 60 A, 230-400. The commercially available reagents and solvents, were used for this work, bromine derivatives of isoxazoles (**3 a-g**) were synthesized by the procedure [26].

{[3- (4-ethoxyphenyl) isoxazol-5-yl] methyl} amine hydrochloride (**2c**) Colourless solid (45 % yield); Mp: 221-222 °C. ¹H NMR (500 MHz, DMSO-d₆): δ = 1.34 (t, *J*= 8.5 Hz, 3H), 4.06 (k, *J*=8.5 Hz, 4H), 4.28 (s, 4H), 7.05 (d, *J*= 10.5 Hz, 2H), 7.10 (s, 1H), 7.76 (d, *J*=10.5 Hz, 2H), 8.90 (s, 3H). ¹³C NMR (125 MHz, DMSO-d₆, ppm): δ = 15.0, 34.3, 63.7, 102.9, 115.5, 120.7, 128.5, 160.6, 162.1, 166.5 ppm; MS (Cl): *m/z* 255 (MH⁺ 100). Anal calcd. for C₁₂H₁₅ClN₂O₂: C, 56.58, H, 5.94, Cl, 13.92, N, 11.00. Found: C, 56.55, H, 5.96, Cl, 13.90 N, 11.04.

{[3-(4-propoxyphenyl) isoxazol-5-yl] methyl} amine hydrochloride (**2d**) Colourless solid (39% yield); Mp: 199-201 °C. ¹H NMR (500 MHz, DMSO-d₆): δ = 0.98 (t, *J*= 9.0 Hz, 3H), 1.69-1.80 (m, 2H), 3.98 (t, *J*=8.0 Hz, 2H), 4.28 (s, 4H), 7.06 (d, *J*= 10.5 Hz, 2H), 7.12 (s, 1H), 7.76 (d, *J*=10.5 Hz, 2H), 8. (s, 3H). ¹³C NMR (125 MHz, DMSO-d₆, ppm): δ = 8.3, 19.9, 31.9, 67.1, 100.4, 113.1, 118.3, 126.1, 158.3, 159.6, 164.0 ppm; MS (Cl): *m/z* 269 (MH⁺ 100). Anal calcd. for C₁₃H₁₇ClN₂O₂: C, 56.58, H, 6.38, Cl, 13.19, N, 10.42. Found: C, 56.56, H, 6.40, Cl, 13.20 N, 11.89.

General procedure for the synthesis of for N,N'-bis[(3-arylisoxazol-5-yl)methyl]sulfamides: Solution (0,01 mol) of sulfonyl chloride in dichloromethane was added slowly to a solution of isoxazole-containing amine hydrochlorides (g, 0.02 mol) in 30 ml dichloromethane at -5-0 ° C in the presence of (g, 0.04 mol) triethylamine for 1.5-2 hours. After adding all sulfonyl chloride, the reaction mixture is stirred for 1.5-2 hours at room temperature. After completion of the reaction, the mixture was filtered off, the solvent was evaporated in vacuo, residue was washed with water (2 x 20 ml). Target products were purified by recrystallization from 96% ethanol.

N,N'-bis[(3-phenylisoxazol-5-yl)methyl]sulfamide (3a) Colourless solid (83% yield); Mp: 165-166 °C. ¹H NMR (500 MHz,

DMSO- d_6): δ = 4.31-4.35 (br. S, 4H), 6.82-6.97 (br. S, 2H), 7.43-7.57 (m. 6H), 7.75-7.88 (m, 4H), 7.88-7.99 (m, 2H). ^{13}C NMR (125 MHz, DMSO- d_6 , ppm): δ = 38.4, 101.2, 127.0, 128.9, 129.6, 130.7, 162.3, 170.7. ppm; MS (CI): m/z 411 (MH^+ 100). Anal calcd. for $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_4\text{S}$: C, 58.53, H, 4.42, N, 13.65, S, 7.81. Found: C, 58.55, H, 4.41, N, 13.63, S, 7.84.

N, N'-bis {[3- (4-methoxyphenyl) isoxazol-5-yl] methyl} sulfamide (**3b**) Colourless solid (77% yield); Mp: 167-168 °C. ^1H NMR (500 MHz, DMSO- d_6): δ = 3.75-3.87 (br. S, 6H), 4.17-4.29 (br. S, 4H), 6.76-6.88 (br. S, 2H), 7.02 (d, J =11.5 Hz, 4H), 7.75 (d, J =11.5 Hz, 4H), 7.83-98 (m, 2H). ^{13}C NMR (125 MHz, DMSO- d_6 , ppm): δ = 38.4, 55.7, 100.9, 114.9, 128.5, 121.3, 161.2, 161.9, 170.3. ppm; MS (CI): m/z 471 (MH^+ 100). Anal calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_6\text{S}$: C, 56.16, H, 4.71, N, 11.91, S, 6.82. Found: C, 56.12, H, 4.74, N, 11.90, S, 6.82.

N, N'-bis {[3- (4-ethoxyphenyl) isoxazol-5-yl] methyl} sulfamide (**3c**) Colourless solid (79% yield); Mp: 164-165 °C. ^1H NMR (500 MHz, DMSO- d_6): δ = 1.34 (t, J = 8.5 Hz, 6H), 4.06 (k, J =8.5 Hz, 4H), 4.15-4.88 (br S, 4H), 6.83 (S, 2H), 6.97 (d, J =11.0 Hz, 4H), 7.73 (d, J =11.0 Hz, 4H), 7.84-7.95 (m, 2H). ^{13}C NMR (125 MHz, DMSO- d_6 , ppm): δ = 15.1, 38.5, 63.7, 100.9, 115.4, 121.2, 128.5, 160.4, 160.9, 170.3 ppm; MS (CI): m/z 499 (MH^+ 100). Anal calcd. for $\text{C}_{24}\text{H}_{26}\text{N}_4\text{O}_6\text{S}$: C, 57.82, H, 5.26,

N, 11.24, S, 6.43. Found: C, 57.80, H, 5.25, N, 11.26, S, 6.45.

N, N'-bis {[3- (4-propoxyphenyl) isoxazol-5-yl] methyl} sulfamide (**3d**) Colourless solid (72% yield); Mp: 159-160 °C. ^1H NMR (500 MHz, DMSO- d_6): δ = 0.98 (t, J = 8.5 Hz, 6H), 1.67-1.79 (m, 4H) 3.96 (t, J =8.5 Hz, 4H), 4.20-4.28 (br S, 4H), 6.83 (S, 2H), 7.00 (d, J =11.0 Hz, 4H), 7.73 (d, J =11.0 Hz, 4H), 7.88-7.96 (m, 2H). ^{13}C NMR (125 MHz, DMSO- d_6 , ppm): δ = 10.8, 22.5, 38.5, 69.6, 100.9, 115.4, 121.2, 128.5, 160.6, 160.9, 170.3 ppm; MS (CI): m/z 526 (MH^+ 100). Anal calcd. for $\text{C}_{26}\text{H}_{30}\text{N}_4\text{O}_6\text{S}$: C, 59.30, H, 5.74, N, 10.64, S, 6.09. Found: C, 59.25, H, 5.71, N, 10.66, S, 6.12.

General procedure for the synthesis of for N,N'-diallyl-bis[(3-aryl isoxazol-5-yl)methyl]sulfamides: To the mixture (0.005 mol) of corresponding sulfamides (3a-d) and (0.011 mol) potassium carbonate in 20 ml DMFA (0.015 mol) of allyl bromide was added. The reaction mixture is stirred at a temperature of 65-70 °C for 4-5 hours. The solvent was removed in vacuo, the residue was washed with water, the product was extracted with 2 x 15 ml of dichloromethane. The extract was dried with anhydrous sodium sulfate and after purification by chromatography (silica gel Merck Grade 9385, 60 A, 230-400, dichloromethane eluent) by evaporation of the solvent and subsequent

recrystallization from 70% aqueous ethanol, the product was isolated.

N,N'-diallyl-bis[(3-phenylisoxazol-5-yl)methyl]sulfamide (**4a**) Colourless solid (91% yield); Mp: 129-130 °C. ¹H NMR (500 MHz, CDCl₃): δ = 3.86 (d, *J*=7.5 Hz, 4H), 4.54 (s, 4H), 5.26-5.37 (m, 4H), 5.78-5.91 (m, 2H), 6.60 (s, 2H), 7.73 (br. s, 6H), 7.77 (br. s, 4H). ¹³C NMR (125 MHz, CDCl₃, ppm): δ = 42.0, 50.5, 102.0, 120.7, 126.8, 128.7, 128.9, 130.2, 131.8, 162.6, 168.2. ppm; MS (CI): *m/z* 490 (MH⁺ 100). Anal calcd. for C₂₆H₂₆N₄O₄S: C, 63.66, H, 5.34, N, 11.42, S, 6.54. Found: C, 63.46, H, 5.40, N, 11.48, S, 6.58.

N,N'-diallyl-*N,N'*-bis{[(3-(4-methoxyphenylisoxazol-5-yl)methyl)]}sulfamide (**4b**) Colourless solid (88% yield); Mp: 108-109 °C. ¹H NMR (500 MHz, DMSO-*d*₆, ppm): δ = 3.29-3.36 (br s, 4H), 3.82-3.90 (br.s, 6H), 4.46-4.60 (br. s, 4H), 5.19-5.37 (m, 4H), 5.75-5.89 (m, 2H), 6.93 (br. s, 2H), 7.04 (d, *J*= 10.5 Hz, 4H), 7.78 (d, *J*=10.5 Hz, 4H). ¹³C NMR (125 MHz, DMSO-*d*₆, ppm): δ = 42.7, 51.1, 55.8, 102.1, 115.0, 120.2, 121.2, 128.6, 133.0, 161.2, 162.0, 169.0. ppm; MS (CI): *m/z* 550 (MH⁺ 100). Anal calcd. for C₂₈H₃₀N₄O₆S: C, 61.08, H, 5.49, N, 10.18, S, 5.82. Found: C, 61.10, H, 5.45, N, 10.19, S, 5.88.

N,N'-diallyl-*N,N'*-bis{[(3-(4-ethoxyphenylisoxazol-5-yl)methyl)]}sulfamide (**4c**) Colourless solid (81% yield); Mp: 104-105 °C. ¹H NMR (500 MHz, CDCl₃): δ = 1.44 (t, *J*=

8.5 Hz, 6H), 3.85 (d, *J*=8.0 Hz, 4H), 4.07 (k, *J*=8.5, 4H), 4.50 (s, 4H), 5.24-5.37 (m, 4H), 5.77-5.90 (m, 2H), 6.52 (s, 2H), 6.93 (d, *J*= 10.5 Hz, 4H), 7.70 (d, *J*=10.5 Hz, 4H). ¹³C NMR (125 MHz, CDCl₃, ppm): δ = 14.8, 41.9, 50.8, 63.6, 101.6, 114.8, 120.6, 120.9, 128.2, 131.8, 160.6, 162.2, 167.8. ppm; MS (CI): *m/z* 578 (MH⁺ 100). Anal calcd. for C₃₀H₃₄N₄O₆S: C, 62.27, H, 5.92, N, 9.68, S, 5.54. Found: C, 62.25, H, 5.88, N, 9.70, S, 5.57.

N,N'-diallyl-*N,N'*-bis{[(3-(4-propoxyphenylisoxazol-5-yl)methyl)]}sulfamide (**4d**) Colourless solid (75% yield); Mp: 99-100 °C. ¹H NMR (500 MHz, CDCl₃): δ = 1.05 (t, *J*=8.0 Hz, 6H), 1.77-1.89 (m, 4H), 3.85 (d, *J*=8.0 Hz, 4H), 3.96 (t, *J*= 8.5, 4H), 4.51 (s, 4H), 5.25-5.35 (m, 4H), 5.76-5.91 (m, 2H), 6.52 (s, 2H), 6.93 (d, *J*= 11.0 Hz, 4H), 7.70 (d, *J*=11.0 Hz, 4H). ¹³C NMR (125 MHz, CDCl₃, ppm): δ = 10.5, 22.5, 42.0, 50.9, 69.6, 101.6, 114.9, 120.6, 120.9, 128.2, 131.9, 160.7, 162.3, 167.9. ppm; MS (CI): *m/z* 606 (MH⁺ 100). Anal calcd. for C₃₂H₃₈N₄O₆S: C, 63.35, H, 6.31, N, 9.23, S, 5.28. Found: C, 63.32, H, 6.28, N, 9.26, S, 5.30.

General procedure for the synthesis of for 2,7-bis[(3-arylisoaxazol-5-yl)methyl]-2,3,6,7-thiadiazepine 1,1-dioxides: To a solution (0.6 mmol) of corresponding diallyl derivatives 4a-d in 15 ml of dry degassed dichloromethane in a dry argon atmosphere (0.028-0.03 mmol, 5% mole) catalyst [Ru] was added. The mixture was kept at room temperature for 10-12 hours.

After completion of the reaction, the target products were isolated from the reaction mixture by column chromatography (Merck Grade 9385, 60 A, 230-400, dichloromethane) followed by evaporation and recrystallization of the products from 70% aqueous ethanol.

2,7-bis{[3-(4-phenylisoxazol-5-yl)methyl]-2,3,6,7-tetrahydro-1,2,7-thiadiazepine 1,1-dioxide (5a)}. Colourless solid (91% yield); Mp: 134-135 °C. ¹H NMR (500 MHz, CDCl₃): δ = 3.91 (s, 4H), 4.62 (s, 4H), 5.84 (s, 2H), 6.65 (s, 2H), 7.45 (s, 6H), 7.80 (d, *J* = 4.5 Hz, 4H). ¹³C NMR (125 MHz, CDCl₃, ppm): δ = 44.8, 45.3, 101.5, 126.8, 128.2, 128.7, 129.0, 130.2, 162.7, 168.2. ppm; MS (CI): *m/z* 463 (MH⁺ 100). Anal calcd. for C₂₄H₂₂N₄O₄S: C, 62.32, H, 4.79, N, 12.11, S, 6.93. Found: C, 62.30, H, 4.77, N, 12.14, S, 6.94.

2,7-bis{[3-(4-methoxyphenyl)isoxazol-5-yl)methyl]-2,3,6,7-tetrahydro-1,2,7-thiadiazepine 1,1-dioxide (5b)} Colourless solid (85% yield); Mp: 139-140 °C. ¹H NMR (500 MHz, CDCl₃): δ = 3.85 (s, 6H), 3.90 (s, 4H), 4.60 (s, 4H), 5.84 (s, 2H), 6.58 (s, 2H), 6.97 (d, *J* = 11.0 Hz, 6H), 7.73 (d, *J* = 11.0 Hz, 4H). ¹³C NMR (125 MHz, CDCl₃, ppm): δ = 44.7, 45.2, 55.4, 101.2, 114.4, 121.1, 128.2, 161.2, 162.3, 168.1. ppm; MS (CI): *m/z* 523 (MH⁺ 100). Anal calcd. for C₂₆H₂₆N₄O₆S: C, 59.76, H, 5.01, N, 10.72, S, 6.14. Found: C, 59.80, H, 5.03, N, 10.68, S, 6.15.

2,7-bis{[3-(4-ethoxyphenyl)isoxazol-5-yl)methyl]-2,3,6,7-tetrahydro-1,2,7-thiadiazepine 1,1-dioxide (5c)} Colourless solid (82% yield); Mp: 129-130 °C. ¹H NMR (500 MHz, CDCl₃): δ = 1.44 (t, *J* = 8.5 Hz, 6H), 3.90 (s, 4H), 4.07 (k, *J* = 8.5 Hz, 4H), 4.59 (s, 4H), 5.84 (s, 2H), 6.58 (s, 2H), 6.95 (d, *J* = 11.0 Hz, 4H), 7.72 (d, *J* = 11.0 Hz, 4H). ¹³C NMR (125 MHz, CDCl₃, ppm): δ = 14.7, 44.7, 45.2, 63.6, 101.2, 114.9, 120.9, 128.2, 160.5, 162.4, 168.1. ppm; MS (CI): *m/z* 551 (MH⁺ 100). Anal calcd. for C₂₈H₃₀N₄O₆S: C, 61.08, H, 5.49, N, 10.18, O, 17.43, S, 5.82. Found: C, 61.05, H, 5.45, N, 10.20, O, 17.46, S, 5.84.

2,7-bis{[3-(4-propoxyphenyl)isoxazol-5-yl)methyl]-2,3,6,7-tetrahydro-1,2,7-thiadiazepine 1,1-dioxide (5d)} Colourless solid (86% yield); Mp: 125-126 °C. ¹H NMR (500 MHz, CDCl₃): δ = 1.05 (t, *J* = 9.0 Hz, 6H), 1.77-1.89 (m, 4H), 3.91 (s, 4H), 3.97 (t, *J* = 8.0 Hz, 4H), 4.60 (s, 4H), 5.84 (s, 2H), 6.58 (s, 2H), 6.96 (d, *J* = 10.5 Hz, 4H), 7.72 (d, *J* = 10.5 Hz, 4H). ¹³C NMR (125 MHz, CDCl₃, ppm): δ = 10.5, 22.5, 44.7, 45.2, 69.6, 101.2, 114.9, 120.2, 128.2, 128.3, 160.8, 162.4, 168.0. ppm; MS (CI): *m/z* 579 (MH⁺ 100). Anal calcd. for C₃₀H₃₄N₄O₆S: C, 62.27, H, 5.92, N, 9.68, S, 5.54. Found: C, 62.24, H, 5.95, N, 9.65, S, 5.56.

Conclusions

Thus, with the help of ring-closing metathesis reactions some of new potentially biologically active isoxazole-containing

derivatives of the thiadiazepine series were synthesized. The comfortable synthetic sequence was worked out and the principle possibility of obtaining the symmetric isoxazole containing derivatives of thiadiazepine was established. The structure of the obtained substances was confirmed by chromatomass spectra, elemental analysis and data of ^1H , ^{13}C NMR spectroscopy.

Acknowledgements

This work has been funded by Scientific Work of Scientific Research of Nas of Ukraine «A development of methods of the new heteroalkenic derivatives synthesis by metathesis reactions», project 2.10.34, 2018-2020.

References

- [1] Drew J. Drug discovery: a historical perspective. Science 2000; 287: 1960-1964.
- [2] Supuran C.T., Scozzafava A. Carbonic Anhydrase Inhibitors. Curr. Med. Chem.- Imm., Endoc. Metab. Agents. 2001; 1(1): 61-97.
- [3] Ogden R. C., Flexner C. W., Ed. in Protease Inhibitors in AIDS Therapy, Marcel Dekker, New York: Basel; 2001, 789.
- [4] Supuran C. T. Indisulam: an anticancer sulfonamide in clinical development Exper Opin. Invest. Drugs. 2003; 12 (2): 283-287.
- [5] Supuran C. T., Scozzafava A., Carbonic anhydrase inhibitors and their therapeutic potential Exp. Opin. Ther. Patents, 2000; 10 (5): 575-600.
- [6] Supuran C. T., Scozzafava A., Menabuoni L., Minicione F., Briganti F., Minicione G., Carbonic anhydrase inhibitors: perfluoroalkyl/aryl-substituted derivatives of aromatic/heterocyclic sulfonamides as topical intraocular pressure-lowering agents with prolonged duration of action. Med. Chem., 2000; 43 (23): 4542-4555.
- [7] Supuran C. T., Casini A., Scozzafava A., Protease inhibitors of the sulfonamide type: anticancer, antiinflammatory, and antiviral agents Med .Res. Rev., 2003; 23 (5): 535-558.
- [8] Shahripour A. B., Plummer M. S., Lunney E. A., Sawyer T. K., Stankovich C. J., Connolly M. K., Rubin J. R., Walker N. P., Brady K. D., Allen H. J., Structure-based design of caspase-1 inhibitor containing a diphenyl ether sulfonamide. Bioorg. Med. Chem. Lett., 2001; 11 (20): 2779-2782
- [9] Roush W. R., Gwaltney S. L., Cheng J., Scheidt K., McKerrow J. H., Hansell E. J., Vinyl Sulfonate Esters and Vinyl Sulfonamides: Potent, Irreversible Inhibitors of Cysteine Proteases. Am. Chem. Soc., 1998; 120 (42): 10994-10995.
- [10] Falgoutyret J., Oballa R. M., Okamoto O., Wesolowski G., Aubin Y., Rydzewski R. M., Prasit P., Riendeau D., Rodan S. B., Percival D. J., Novel, Nonpeptidic Cyanamides as Potent and Reversible Inhibitors of Human Cathepsins K and L. Med. Chem., 2001, 44 (1), 94-104.
- [11] Vullo D., Franchi M., Gallori E., Pastorec E., Scozzafava A., Pastorekova S., Supuran C., Carbonic anhydrase inhibitors: inhibition of the tumor-associated isozyme IX with aromatic and heterocyclic sulfonamides. Bioorg. Med. Chem. Lett., 2003; 13 (6): 1005-1009.
- [12] Debnath S., Mondal S., Sultams: Recent Syntheses and Applications Eur. J. Org. Chem., 2018; 8: 933-956.
- [13] Jadhav P. K., Woerner F. J., Synthesis of 8-membered cyclic sulfamides: Novel HIV-1 protease inhibitors. Tetrahedron Lett. 1995; 36 (36): 6383-6386.
- [14] Hulten J., Bonham N. M., Nillroth U., Hansson T., Zuccarello G., Bouzide A., Aqvist J., Classon B., Danielson U. H., Karlen A., Kvarnstrom I., Samuelson B., Hallberg A., Cyclic HIV-1 Protease Inhibitors Derived

from Mannitol: Synthesis, Inhibitory Potencies, and Computational Predictions of Binding Affinities *J. Med. Chem.*, 1997; 40 (6): 885-897.

[15] Hulten J., Andersson H. O., Schaal W., Danielson H. U., Classon B., Kvarnstrom I., Karlen A., Unger T., Samuelsson B. and Hallberg A., Inhibitors of the C2-Symmetric HIV-1 Protease: Nonsymmetric Binding of a Symmetric Cyclic Sulfamide with Ketoxime Groups in the P2/P2' Side Chains *J. Med. Chem.*, 1999; 42 (20): 4054-4061.

[16] Ax A., Schaal W., Vrang L., Samuelson B., Hallberg A., Karlen A., A. Cyclic sulfamide HIV-1 protease inhibitors, with sidechains spanning from P2/P2' to P1/P1'. *Bioorganic & Medicinal Chemistry*, 2005; 13 (3): 755-764.

[17] Kenji T., Yoshiyuki T., Tsutomu I., Takashi K., Toshiyuki A., Shuichi S., T. Yoshinori T., Masafumi I. Shionogi & Co., Ltd. Osaka-shi, Osaka 541-0045 (JP). HIV Replication inhibitor. Pat EP 2 952 503 A1. 2015 December 9.

[18] Kano H., Adachi I., Kido R., Hiroze K. Isoxazoles. XVIII. Synthesis and Pharmacological Properties of 5-Aminoalkyl- and 3-Aminoalkylisoxazoles and Related Derivatives *J. Med. Chem.* 1967; 10 (3): 411-118.

[19] Selvam C., Jachak S. M., Tilagovathi R., Chakrarti A. K. Design, synthesis, biological evaluation and molecular docking of curcumin analogues as antioxidant, cyclooxygenase inhibitory and anti-inflammatory agents *Bioorg. Med. Chem. Lett.*, 2005; 15 (7): 1793-1997.

[20] Talley J. J., Brown D. L., Carter J. S., et al. 4-[5-Methyl-3-phenylisoxazol-4-yl]- benzenesulfonamide, valdecoxib: a potent and selective inhibitor of COX-2. *J. Med. Chem.*, 2000; 43 (5): 775-777.

[21] Pradeepkumar Y., M. Ruthu M., Madhusudhana chetty C., Prasanthi G., Jayasankar Reddy V. Pharmacological activities of isoxazole derivatives *Journal of Global Trends in Pharmaceutical Science*, 2011; 2 (1): 55-62.

[22] Trnka T. M., Grubbs R. H. The development of L2X2Ru=CHR olefin metathesis catalysts: an organometallic success story. *Acc. Chem. Res.*, 2001; 34 (1): 18-29.

[23] Donohoe T.J., Orr A. J., Gosby K., Bingham M. A Metathesis Approach to Aromatic Heterocycles, *Eur. J. Org. Chem.*, 2005; 10: 1969-1971.

[24] Pei Y., Wickham O. S., Regioselective syntheses of 3-aminomethyl-5-substituted isoxazoles: A facile and chemoselective reduction of azide to amine by sodium borohydride using 1,3-propanedithiol as a catalyst *Tetrahedron Letters* 1993; 34 (47): 7509-7512.

[25] Yuxiu L., Zhipeng C., Bin L., Baoli C., Yonghong L., Qingmin W. Design, synthesis, and herbicidal activities of novel 2-cyanoacrylates containing isoxazole moieties *Journal of Agricultural and Food Chemistry*, 2010; 58 (5): 2685-2689.

[26] Pavliuk O. V., Holovatiuk V. M., Yu. V. Bezugly Yu. V., Kashkovsky V. I. Synthesis of new sulfonylamide derivatives of isoxazole via ring-closing metathesis *Dopov. Nac. akad. nauk Ukr.*, 2015; 3: 127-134.