Ring closing metathesis strategies to isoxazole containing thiadiazepines

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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 substitutents. The structure of the obtained substances was confirmed by ^{1}H, ^{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], acetozolamide [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

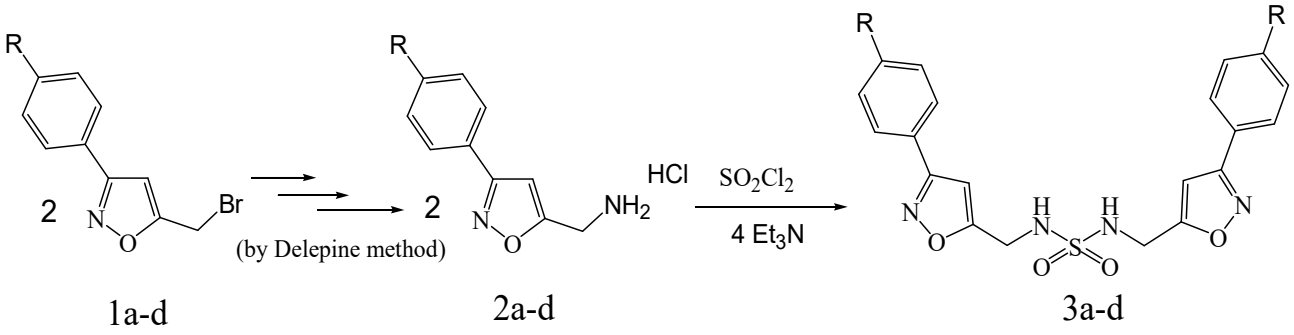
Derivative,[18], [19], [20], [21] we offered a way of obtaining new isoxazole-containing derivatives of thiodiazepines using as key stage of the synthesis ring closing metathesis reactions [22], [23].

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 Delepin (**Scheme 1**).

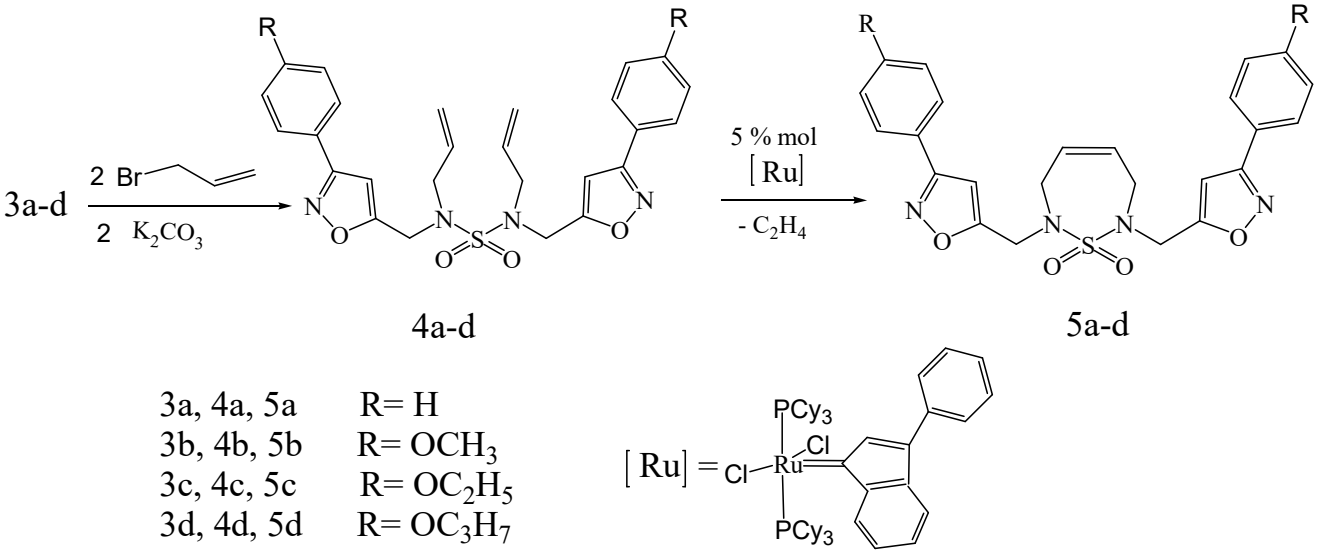


1a, 2a, 3a R= H
1b, 2b, 3b R= OCH_3
1c, 2c, 3c R= OC_2H_5
1d, 2d, 3d R= OC_3H_7

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 sulfuryl chloride in the presence of triethylamine. Acylation of amines with sulfuryl chloride was carried out in solutions of dichloromethane at a temperature of about 0 ºC 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, ^{1}H, ^{13}C 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 ºC 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 ^{1}H, ^{13}C NMR spetra. Ring-closing metathesis reactions of the derivative (**4a-d**) were carried our in solutions of dry degassed dichloromethane in the atmosphere of dry argon at a temperature of 25-30 ºC for 10-12 hours using a ruthenium-carbene catalyst ([**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 ^{1}H, ^{13}C NMR spectra, elemental analysis. The disappearance of the signals of four protons of terminal $=CH_2$- groups in the region of 5.33 ppm and two allilic –CH= 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 spetra of each of the compounds (**5a-d**), there is a signal of C atoms at 127.7 ppm, characteric of the sp^2 hybridized carbon atoms of the seven-membered ring, and there is no signal of the carbon atoms of the terminal $=CH_2$-groups at 120.7 ppm, observed in the spectra of the starting diallyl derivatives (**4a-d**).

Experimental part

General information: ^{1}H 1H (500 MHz) and 13C (125 MHz) NMR spectra were recorded on Bruker Avance DRX 500 spectrometer in $CDCl_3$, DMSO–d6 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-H_2O 95: 5, 0,1% aqueous CF_3COOH, B) 0,1% aqueous CF_3COOH; 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 ºC. ^{1}H NMR (500 MHz, DMSO-d_6): 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). ^{13}C NMR (125 MHz, DMSO-d_6, 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 $C_{12}H_{15}ClN_2O_2$: 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 ºC. ^{1}H NMR (500 MHz, DMSO-d_6): 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). ^{13}C NMR (125 MHz, DMSO-d_6, 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 $C_{13}H_{17}ClN_2O_2$: 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 sulfuryl 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 sulfuryl 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 ºC. ^{1}H 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 (Cl): *m/z* 411 (MH^+ 100). Anal calcd. for $C_{20}H_{18}N_4O_4S$: 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 ºC. ^{1}H 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 (Cl): *m/z* 471 (MH^+ 100). Anal calcd. for $C_{22}H_{22}N_4O_6S$: 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 ºC. ^{1}H 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 (Cl): *m/z* 499 (MH^+ 100). Anal calcd. for $C_{24}H_{26}N_4O_6S$: 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 ºC. ^{1}H 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 (Cl): *m/z* 526 (MH^+ 100). Anal calcd. for $C_{26}H_{30}N_4O_6S$: 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-arylisoxazol-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 stired at a temperature of 65-70 ºC 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 subsesequent

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. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$, 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 (Cl): *m/z* 490 (MH^+ 100). Anal calcd. for $C_{26}H_{26}N_4O_4S$: 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. ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ = 3.29-3.36 (br s,4H), 3.82-3.3.90 (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). ^{13}C 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 (Cl): *m/z* 550 (MH^+ 100). Anal calcd. for $C_{28}H_{30}N_4O_6S$: 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. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$, 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 (Cl): *m/z* 578 (MH^+ 100). Anal calcd. for $C_{30}H_{34}N_4O_6S$: 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. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$, 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 (Cl): *m/z* 606 (MH^+ 100). Anal calcd. for $C_{32}H_{38}N_4O_6S$: 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-arylisoxazol-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 colum 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-phenylisoxazol-5-yl)methyl}2,3,6,7-tetrahydro-1,2,7-thiadiazepine 1,1-dioxide **(5a).** Colourless solid (91% yield); Mp: 134-135 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): *δ* = 44.8, 45.3, 101.5, 126.8, 128.2, 128.7, 129.0, 130.2, 162.7, 168.2. ppm; MS (Cl): *m/z* 463 (MH^+ 100). Anal calcd. for $C_{24}H_{22}N_4O_4S$: 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 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): *δ* = 44.7, 45.2, 55.4, 101.2, 114.4, 121.1, 128.2, 161.2, 162.3, 168.1. ppm; MS (Cl): *m/z* 523(MH^+ 100). Anal calcd. for $C_{26}H_{26}N_4O_6S$: 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 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$, 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 (Cl): *m/z* 551 (MH^+ 100). Anal calcd. for $C_{28}H_{30}N_4O_6S$: 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 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$, 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 (Cl): *m/z* 579 (MH^+ 100). Anal calcd. for $C_{30}H_{34}N_4O_6S$: 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 synthesited. The comfortable synthetic sequence was worked out and the principle possibility of obtaining the symmetric isoxasole containing derivatives of thiadiazepine was established. The structure of the obtained substances was confirmed by chromatomass spectra, elemental analysis and data of ^{1}H, ^{13}C NMR spectroscopy.

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