HETEROCYCLES 31. SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF 5-(PYRIDIN-4-YL)-1,3,4-OXADIAZOLE-2-THIOL, 5-(PYRIDIN-4-YL)-1,3,4-THIADIAZOLE-2-THIOL AND 5-(PYRIDIN-4-YL)-1,2,4-TRIAZOLE-3-THIOL DERIVATIVES

ALEXANDRA TOMA[1], DENISA HAPĂU[1], LAURIAN VLASE[2], CRISTINA MOGOŞAN[3], VALENTIN ZAHARIA[1]

[1]Department of Organic Chemistry
[2]Department of Pharmaceutical Technology and Biopharmacy
[3]Department of Pharmacology, Pysiology and Physiopathology
Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Abstract

The pyridine ring and the heterocyclic pentaatomic systems: 1,3-thiazole, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole are known for their biological potential and can be found not only in naturally occurring compounds, but also in synthetic compounds with anti-inflammatory, analgesic, anticancer, antibacterial and antifungal properties. Based on these considerations, we obtained some thioethers containing the previously mentioned heterocyclic systems and we evaluated their anti-inflammatory activity using carrageenan-induced rat paw edema assay.

Keywords: anti-inflammatory activity, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, thioethers.

Introduction

Heterocyclic compounds are well known for their pharmacological potential that is exploitable in the synthesis of new bioactive molecules. Moreover, nowadays, heterocyclic chemistry becomes more and more advanced in the development of new polyheterocyclic compounds. These compounds are extremely valuable because they possess not only the pharmacological potential owned by the heterocycles themselves, but also a new one due to the reciprocal influence between the contained heterocycles.

Azolic derivatives such as thiazole, triazole, oxadiazole and thiadiazole are pharmacologically useful compounds and have been intensely investigated for various biological activities, due to their promising application in the medicinal chemistry. A significant antimicrobial activity has been reported for some 1,3-thiazoles [1,2]; 1,3,4-oxadiazoles [3-5], 1,3,4-thiadiazoles [6] and 1,2,4-triazoles [7]. A few 1,3-thiazole derivatives have been evaluated for their anti-inflammatory activity [8,9]. Some 1,3,4-oxadiazole derivatives have been reported as stem cell proliferation activators [10] and also different enzime activators [11], while others have shown an important cytostatic activity [12], anti-inflammatory and analgesic activity [13,14] or analgesic activity [15]. 1,3,4-thiadiazole derivatives are known for their various biological activities such as: anticancer [16], anti-depressant [17], enzime inhibitors [18] and anti-inflammatory [19], while the 1,2,4-triazoles have been investigated for their anti-inflammatory activity [20,21,22]. Also, several heterocyclic thioethers have been reported as potent anti-inflammatory agents [14,19,20].

Based on these considerations, we proposed to obtain some polyheterocyclic thioethers containing the azolic rings 1,3-thiazole, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-tiadiazole and to evaluate their anti-inflammatory activity. The compounds were purified by recrystallization or by column chromatography and characterized from a physical and chemical point of view: melting point, ^{1}H RMN, ^{13}C RMN and MS spectra. Some of the synthesised thioethers were evaluated for their anti-inflammatory activity using carrageenan-induced rat paw edema assay.

Materials and methods

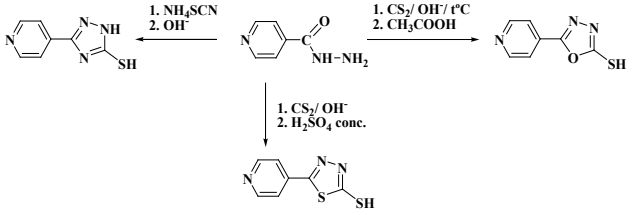
All used reagents and solvents were purchased from Merck. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-D_6 solution on a Brucker Avance DPX spectrometer operating at 300, 400 and 75 MHz, respectively. Chemical shifts on the δ scale are expressed in ppm values from TMS as internal standard. Mass spectra were recorded on Agilent 1100 Ion Trap mass spectrometer operating at 70 eV.

Adresses for correspondence: tomaalecsandra@yahoo.com; vzaharia@umfcluj.ro

Thin layer chromatography was carried out using Merck Kieselgel 60 F254 sheets. Preparative chromatographic separations were performed using column chromatography on Merck Kieselgel 60 (63-200 μm). Melting points were determined on open glass capillaries using an Electrothermal IA 9000 digital melting point apparatus.

Chemical synthesis of the polyheterocyclic compounds

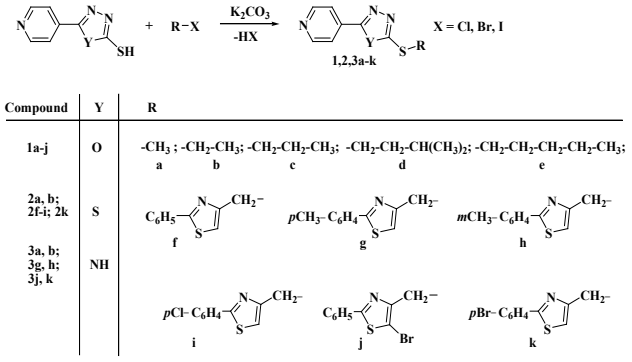
As shown in Scheme 1, the bis-heterocyclic precursors where synthesised as previously described in the literature [23,24], starting from isonicotinic hydrazide.



Scheme 1. The synthesis of 5-(pyridin-4-yl)-1,3,4-oxadiazole-2-thiol, 5-(pyridin-4-yl)-1,3,4-thiadiazole-2-thiol and 5-(pyridin-4-yl)-1,2,4-triazole-3-thiol.

The thiazolic halogenated compounds (2-aryl-4-chloromethyl-thiazole and 2-aryl-4-chloromethyl-5-bromo-thiazole) have been obtained by Hantzsch condesation of various aryl-thioamides and 1,3-dichloropropan-2-one according to the literature [25,26].

The new polyheterocyclic compounds were synthesized as described in Scheme 2 [23,27-30].



Scheme 2. The synthesis of the corresponding thioethers **1,2,3a-k.**

General procedure for obtaining 4-[5-(substituted thio)-1,3,4-oxadiazol-2-yl]pyridine (1a – j):

To a stirred solution of 4-(5-thio-1,3,4-oxadiazole-2-yl)pyridine (0.18 g, 1 mmol) and K_2CO_3 (0.07 g, 0.5 mmol) in 10 ml absolute ethanol, the correspondig halogenated compound was added (1 mmol). The reaction mixture was stirred at room temperature for 24 h. The formed precipitate was filtred and washed with ethanol. The newly obtained compounds were purified by recrystallization or by column chromatography. Compounds **1a,b** are allready synthesised and characterized [27,23]. Compounds **1c**, **1f**, **1h**, **1j** were recrystallised from ethanol – water and compounds **1g** and **1i** from DMF – water. Compounds **1d – e** were purified by column chromatography using a mixture of dichloromethane and acetone (1:0.5 v/v).

4-(5-(methyllthio)-1,3,4-oxadiazol-2-yl)pyridine (**1a**) [27]**:** Yield: 71%; solid; m.p.: 102-102.6ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.80 (s, 3H); 7.85 (dd, 2H); 8.78 (dd, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6; 119.9; 130.7; 150.8; 163.9; 166.7; ESI$^+$-MS: M^+ found (M^+ calculated for $C_8H_7N_3OS$): 194.1 (193.03).

4-(5-(ethyllthio)-1,3,4-oxadiazol-2-yl)pyridine (**1b**) [23]**:** Yield: 64%; solid; m.p.: 75-75.3ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53 (t, 3H); 3.33 (q, 2H); 7.84 (dd, 2H); 8.80 (dd, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6; 267.0; 119.9; 130.7; 150.4; 163.8; 166.0; ESI$^+$-MS: M^+ found (M^+ calculated for $C_9H_9N_3OS$): 208.2 (207.04).

4-(5-(propylthio)-1,3,4-oxadiazol-2-yl)pyridine (**1c):** Yield: 57%; solid; m.p.: 49-50ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, 3H); 1.75 (m, 2H); 3.26 (t, 2H); 7.85 (dd, 2H); 8.80 (dd, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1; 22.6; 34.5; 120.0; 130.7; 150.8; 163.7; 165.3; ESI$^+$-MS: M^+ found (M^+ calculated for $C_{10}H_{11}N_3OS$): 222.3 (221.06).

4-(5-(isopentylthio)-1,3,4-oxadiazol-2-yl)pyridine (**1d):** Yield: 88%; liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, 6H); 1.72-1.76 (m, 3H); 3.34 (t, 2H); 7.85 (dd, 2H); 8.80 (dd, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1; 27.4; 30.8; 37.9; 120.0; 130.7; 151.0; 163.7; 165.3; ESI$^+$-MS: M^+ found (M^+ calculated for $C_{12}H_{15}N_3OS$): 250.50 (249.09).

4-(5-(pentylthio)-1,3,4-oxadiazol-2-yl)pyridine (**1e):** Yield: 55%; liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, 3H); 1.33-1.40 (m, 2H); 1.42-1.49 (m, 2H); 1.84-1.87 (m, 2H); 3.32 (t, 2H); 7.85 (dd, 2H); 8.79 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9; 22.1; 28.8; 30.7; 32.6; 120.0; 130.7; 150.8; 163.7; 166.3; ESI$^+$-MS: M^+ found (M^+ calculated for $C_{12}H_{15}N_3OS$): 250.50 (249.09).

4-(5-((2-phenylthiazol-4-yl)methylthio)-1,3,4-oxadiazol-2-yl)pyridine (**1f):** Yield: 43%; solid; m.p.: 117-119ºC ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.71(s, 2H); 7.41-7.44 (m, 4H); 7.84-7.85 (dd, 2H); 7.89-7.93 (m, 2H); 8.78 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.2; 117.7; 120.0; 126.6; 129.0; 130.3; 130.6; 133.2; 150.8; 151.0; 164.1; 165.5; 168.8; ESI$^+$-MS: M^+ found (M^+ calculated for $C_{17}H_{12}N_4OS_2$): 353.50 (352.04).

4-(5-((2-*p*-tolylthiazol-4-yl)methylthio)-1,3,4-oxadiazol-2-yl)pyridine (**1g):** Yield: 96%; solid; m.p.: 127.9-128.9ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H); 4.69 (s, 2H); 7.22 (d, 2H); 7.37 (s, 1H); 7.79 (dd, 2H); 7.84 (d, 2H); 8.79 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4; 32.3; 117.2; 120.0; 126.5; 129.6; 130.5; 130.6; 140.6; 150.7; 150.8; 164.1; 165.6; 169.0; ESI$^+$-MS: M^+ found (M^+ calculated for $C_{18}H_{14}N_4OS_2$): 367.40 (366.06).

4-(5-((2-*m*-tolylthiazol-4-yl)methylthio)-1,3,4-oxadiazol-2-yl)pyridine (1h): Yield: 46%; solid; m.p.: 106.4-108.8ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3H); 4.70 (s, 2H); 7.24 (d, 1H); 7.31 (t, 1H); 7.40 (s, 1H); 7.69 (d, 1H); 7.74 (s, 1H); 7.84 (dd, 2H); 8.78 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3; 32.3; 117.6; 120.0; 123.8; 127.0; 128.9; 130.6; 131.1; 133.1; 138.8; 150.8; 150.9; 164.1; 165.5; 169.0; ESI$^+$-MS: M^+ found (M^+ calculated for $C_{18}H_{14}N_4OS_2$): 367.40 (366.06).

4-(5-((2-(4-chlorophenyl)thiazol-4-yl)methylthio)-1,3,4-oxadiazol-2-yl)pyridine (1i): Yield: 67%; solid; m.p.: 149.7-150.4ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.69 (s, 2H); 7.37-7.41 (m, 2H); 7.43 (s, 1H); 7.82-7.87 (m, 4H); 8.78 (dd, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.1; 118.0; 120.0; 127.7; 129.2; 130.5; 131.7; 136.3; 150.9; 151.2; 164.1; 165.4; 167.3; ESI$^+$-MS: M^+ found (M^+ calculated for $C_{17}H_{11}ClN_4OS_2$): 387.70 (386.01).

4-(5-((5-bromo-2-phenylthiazol-4-yl)methylthio)-1,3,4-oxadiazol-2-yl)pyridine (1j): Yield: 72%; solid; m.p.: 167.1-168.6ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68 (s, 2H); 7.37-7.44 (m, 3H); 7.78-7.82 (m, 2H); 7.86 (d, 2H); 8.79 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.2; 107.6; 120.1; 126.2; 129.1; 130.6; 130.8; 132.6; 149.4; 150.8; 164.2; 165.0; 168.4; ESI$^+$-MS: M^+ found (M^+ calculated for $C_{17}H_{11}BrN_4OS_2$): 431.20 (429.95).

General procedure for obtaining 4-[5-(substituted thio)-1,3,4-thiadiazol-2-yl] pyridine (2a – b; 2f – i; 2k):

To a stirred solution of 5-(4-pyridyl)-2-thio-1,3,4-thiadiazole (0.19 g, 1 mmol) and K_2CO_3 (0.07 g, 0.5 mmol) in 10 ml absolute ethanol, the correspondig halogenated compound was added (1 mmol). The reaction mixture was stirred at room temperature for 24 h. The formed precipitate was filtred and washed with ethanol. The newly obtained compounds were purified by recrystallization. Compounds **2a, b** have been allready obtained [28,29]. Compounds **2f** and **2h** were recrystallised from DMF – water, compounds **2g** and **2i** from DMF – ethanol and compound **2k** from ethanol.

4-(5-(methyllthio)-1,3,4-thiadiazol-2-yl)pyridine (2a) [28]; Yield: 53%; solid; m.p.: 123.9-126.5ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.85 (s, 3H); 7.74 (dd, 2H); 8,74 (dd, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4; 121.2; 136.9; 150.8; 165.5; 168.5. ESI$^+$-MS: M^+ found (M^+ calculated for $C_8H_7N_3S_3$): 210.3 (209.08).

4-(5-(methyllthio)-1,3,4-thiadiazol-2-yl)pyridine (2b) [29]; Yield: 52%; solid; m.p.: 102.8-105.5ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 (t, 3H); 3.41 (q, 2H); 7.74 (dd, 2H); 8,74 (dd, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4; 28.6; 121.2; 136.9; 150.8; 165.5; 167.6. ESI$^+$-MS: M^+ found (M^+ calculated for $C_9H_9N_3S_3$): 224.2 (223.02).

4-(5-((2-phenylthiazol-4-yl)methylthio)-1,3,4-thiadiazol-2-yl)pyridine (2f): Yield: 55%; solid; m.p.:148.2-150.5ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.80 (s, 2H); 7,38 (s, 1H); 7.40-7.45 (m, 3H); 7.74 (dd, 2H); 7,89-7,95 (m, 2H); 8,74 (dd, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.5; 117.6;121.3; 126.5; 128.9; 130.2; 133.2; 136.8; 150.8; 151.4; 166.8; 166.7; 168.7. ESI$^+$-MS: M^+ found (M^+ calculated for $C_{17}H_{12}N_4S_3$): 369.6 (368.02).

4-(5-((2-*p*-tolylthiazol-4-yl)methylthio)-1,3,4-thiadiazol-2-yl)pyridine (2g): Yield: 50%; solid; m.p.: 160.3-161.8ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H); 4.78 (s, 2H); 7.34 (s, 1H); 7.22-7.26 (t, 2H); 7.74 (dd, 2H); 7.80 (d, 2H); 8.74 (dd, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4; 33.6; 117.1; 121.3; 126.5; 129.6; 130.6; 136.8; 140.6; 150.8; 151.2; 166.0; 166.7; 168.8. ESI$^+$-MS: M^+ found (M^+ calculated for $C_{18}H_{14}N_4S_3$): 383.2 (382.03).

4-(5-((2-*m*-tolylthiazol-4-yl)methylthio)-1,3,4-thiadiazol-2-yl)pyridine (2h): Yield: 60%; solid; m.p.: 140-141ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3H); 4.79 (s, 2H); 7.37 (s, 1H); 7.22-7.26 (m, 2H); 7.29-7.34 (m, 2H); 7.71-7.76 (m,2H); 8.74 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3; 33.5; 117.5; 121.3; 123.8; 127.0; 128.8; 131.0; 133.1; 136.8; 138.78; 150.8; 151.2; 166.0; 166.7; 168.9; ESI$^+$-MS: M^+ found (M^+ calculated for $C_{18}H_{14}N_4S_3$): 383.2 (382.03).

4-(5-((2-*p*-clorophenyllthiazol-4-yl)methylthio)-1,3,4-thiadiazol-2-yl)pyridine (2i): Yield: 81%; solid; m.p.: 166-169ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79 (s, 2H); 7.39-7.42 (m, 3H); 7.74 (dd, 2H); 7.84-7.88 (m, 2H); 8.75 (dd, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.3; 117.9; 121.2; 127.7; 129.5; 131.7; 136.2; 136.7; 150.8; 151.7; 166.1; 166.5; 166.2. ESI$^+$-MS: M^+ found (M^+ calculated for $C_{17}H_{11}ClN_4S_3$): 403.7 (401.98).

4-(5-((2-*p*-bromophenylthiazol-4-yl)methylthio)-1,3,4-thiadiazol-2-yl)pyridine (2k): Yield: 44%; solid; m.p.: 169.1-169.7ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79 (s, 2H); 7.41 (s, 1H); 7.54-7.58 (m, 2H); 7.74 (dd, 2H);7.77-7.82 (m, 2H); 8.75 (dd, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.3; 117.9; 121.2; 124.5; 127.7; 128.0; 132.1; 136.7; 150.8; 151.7; 166.1; 166.5; 167.3; ESI$^+$-MS: M^+ found (M^+ calculated for $C_{17}H_{11}BrN_4S_3$): 447.20 (445.93).

General procedure for obtaining 4-[5-(substituted thio)-1,2,4-triazol-3-yl] pyridine (3a, b; 3g, h; 3j; 3k):

To a stirred solution of 5-(4-pyridyl)-3-thio-1,2,4-triazole (0.18 g, 1 mmol) and K_2CO_3 (0.07 g, 0.5 mmol) in 10 ml absolute ethanol, the correspondig halogenated compound (1mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The formed precipitate was filtred and washed with ethanol. The newly obtained compounds were purified by recrystallization. Compound **3b** has been allready obtained [30]. Compounds **3g, h** and **3j** were recrystallised from ethanol – water, compound **3k** from ethanol and compound **3a** from water.

4-(5-(methylthio)-1,2,4-triazol-3-yl)pyridine (3a): Yield: 53%; solid; m.p.: 166.1-167.9ºC; ^{1}H NMR (300 MHz, DMSO-D_6): δ = 2.65 (s, 3H); 7.88 (dd, 2H); 8.69 (d, 2H); ^{13}C NMR (75 MHz, DMSO-D_6): δ = 14.2;

119.8; 136.5; 150.4; 156.4; 157.4; ESI$^+$-MS: M^+ found (M^+ calculated for $C_8H_8N_4S$): 193.3 (192.05).

4-(5-(ethylthio)-1,2,4-triazol-3-yl)pyridine (3b) [30]: Yield: 54%; solid; m.p.: 147.7-148.8ºC; ^{1}H NMR (300 MHz, DMSO-D_6): δ = 1.34 (t, 3H); 3.19 (q, 2H); 7.89 (dd, 2H); 8.69 (d, 2H); ^{13}C NMR (75 MHz, DMSO-D_6): δ = 15.0; 26.1; 119.8; 136.6; 150.4; 154.4; 157.5; ESI$^+$-MS: M^+ found (M^+ calculated for $C_9H_{10}N_4S$): 207.3 (206.06).

4-(5-((2-*p*-tolylthiazol-4-yl)methylthio)-1,2,4-triazol-3-yl)pyridine (3g): Yield: 46%; solid; m.p.: 187.4-188.3ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3H); 4.37 (s, 2H); 7,20 (s, 1H); 7.31 (d, J = Mz, 2H); 7.82 (d, 2H); 7.99-8.01 (dd, 2H); 8.68-8.70 (dd, 2H); 14.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4; 32.4; 116.3; 120.5; 120.6; 126.4; 129.7; 130.0; 138.3; 141.5; 150.1; 152.7; 160.7; 170.5. ESI$^+$-MS: M^+ found (M^+ calculated for $C_{18}H_{15}N_5S_2$): 366.4 (365.07).

4-(5-((2-*m*-tolylthiazol-4-yl)methylthio)-1,2,4-triazol-3-yl)pyridine (3h): Yield: 32%; solid; m.p.: 178.1-182.2ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47 (s, 3H); 4.38 (s, 2H); 7.31 (s, 1H); 7.39-7.42 (m, 2H); 7.76 (d, 2H); 7.99-8.01 (dd, 2H); 8.68-8.70 (dd, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4; 32.4; 116.7; 120.5; 123.6; 127.2; 129.3; 131.8; 132.3; 138.2; 138.7; 139.2; 143.3; 150.8; 152.8; 154.2. ESI$^+$-MS: M^+ found (M^+ calculated for $C_{18}H_{15}N_5S_2$): 366.6 (365.07).

4-(5-((2-*p*-bromophenylthiazol-4-yl)methylthio)-1,2,4-triazol-3-yl)pyridine (3k): Yield: 68%; solid; m.p.: 105.4-108,5ºC; ^{1}H NMR (300 MHz, DMSO-D_6): δ = 4.61 (s, 2H); 7.64 (d, 2H) – overlapped with 7.64 (s, 1H); 7.80 (d, 2H); 7.91 (dd, 2H); 8.70 (d, 2H); ^{13}C NMR (75 MHz, DMSO-D_6): δ = 31.7; 118.3; 119.9; 123.5; 127.8; 128.0; 131.9; 132.1; 136.1; 150.4; 152.7; 165.8; 167.9; ESI$^+$-MS: M^+ found (M^+ calculated for $C_{17}H_{12}BrN_5S_2$): 430.2 (428.97).

4-(5-((5-bromo-2-phenylthiazol-4-yl)methylthio)-1,2,4-triazol-3-yl)pyridine (3j): Yield: 49%; solid; m.p.: 222.2-225.3ºC; ^{1}H NMR (300 MHz, DMSO-D_6): δ = 4.55 (s, 2H); 7.46-7.49 (m, 3H); 7.82 (d, 2H); 7.91 (dd, 2H); 8.7 (d, 2H); ^{13}C NMR (75 MHz, DMSO-D_6): δ = 30.8; 106.8; 119.9; 125.8; 129.3; 130.9; 132.0; 137.4; 150.4; 151.2; 163.3; 166.9; ESI$^+$-MS: M^+ found (M^+ calculated for $C_{17}H_{12}BrN_5S_2$): 430.7 (428.97).

The evaluation of the anti-inflammatory activity

Some of the newly synthesised thioethers were tested in order to evaluate their anti-inflammatory activity, by using the carrageenan-induced rat paw edema assay. Male rats Winstar breed weighing 140-200g each were placed into 11 groups of 6 rats. The animals were housed in standard conditions with food ad water *ad libitum*. The control group received intraperitoneally (i.p.) 1 ml vehicle (distilled water and Tween 80). The standard group received diclofenac 20 mg/kg i.p. as reference drug. The tested compounds with doses of 50 mg/rat were injected i.p. in the nine treated groups. The volume of solution for intraperitoneal injection was 1 ml in all cases.

Thirty minutes after administration, the rats hind left paw volume was measured using an Ugo Basile 7140 plethysmometer. Then, the inflammation was induced by injecting 0,1 ml carrageenan solution 1%, intraplantar. Rats edema were evaluated by measuring the rat paw volume at hourly intervals from 1 to 4 hours.

The inhibition percent was calculated as:

% Inhibition of edema = (1-Ēt/Ēm)x100, where Ēt represents the average value of the edema in treated groups in 1 – 4 hours after carragenan injection (in ml), while Ēm represents the average value of the edema in control group in 1 – 4 hours after carrageenan injection (in ml).

Results and discussion

Chemical synthesis of the polyheterocyclic compounds

The new polyheterocyclic compounds were synthesized by previously described methods [23,27-30], by the alkylation of the thiol group with various halogenated compounds, under basic conditions (Scheme 2).

The structures of all new obtained thioethers were confirmed by their spectral analysis (^{1}H NMR, ^{13}C NMR and MS). In the ^{1}H NMR spectra, the aromatic protons from the pyridine ring (H_A and H_B) appeared as two doublets and, in most cases, each signal is split into another doublet because of the magnetic unequivalence between the two H_A protons (positions 2 and 6) and respectively the two H_B protons (positions 3 and 5). This is due to the molecular rigidity, explained by the π-π conjugation between the two adjacent heterocyclic ring systems. The most deshielded

Table I. Anti-inflammatory activities of some of the obtained compounds in carrageenan-induced rat paw edema.

Entry	Compound	% inhibition 1h	% inhibition 2h	% inhibition 3h	% inhibition 4h
1	**Diclofenac**	-51.35	36.75	15.82	16.87
2	**1a**	-27.02	**40.17**	**55.06**	**37.50**
3	**1i**	5.40	26.49	26.58	25.00
4	**1j**	13.51	22.22	32.91	34.37
5	**2b**	-102.70	11.96	17.72	-1.87
6	**2f**	-43.24	**30.76**	**35.44**	**35.62**
7	**2h**	-56.75	**38.46**	**48.10**	**44.37**
8	**3g**	-110.80	28.20	17.08	11.87
9	**3k**	-56.75	-16.23	6.96	-20.00
10	**3i**	-74.00	-13.67	-1.26	-3.75

aromatic protons were found to be the most closer to the electronegative nitrogen (H_A at δ 8.69-8.80 ppm). The ^{1}H NMR spectra for compounds **1a-e**; **2a,b**; **3a,b** showed different characteristic aliphatic signals, due to the presence of the alkylthio- moiety (methylthio-, ethylthio-, propylthio-, isopentenylthio-, pentylthio-). For compounds **1f-i**; **2f-k**; **3g-k**, the CH in the 5th position of the thiazole ring appeared in the aromatic region as singlet at δ 7.20-7.64 ppm, while the protons from the –S-CH_2- group appeared as singlet in the aliphatic region at δ 4.37-4.80 ppm. ^{13}C NMR and MS analysis also confirmed the structures of the obtained thioethers. In the case of compounds **3a-j**, the formation of the S-alkylated products and not of those N-alkylated or N,S-dialkylated, was confirmed by spectral analyses.

The evaluation of the anti-inflammatory activity

As shown in **Table I,** compound **1a, 2f and 2h** were found to be more effective than diclofenac after 2, 3 and 4 hours from the carrageenan-iduced edema, while compounds **1i, 1j and 2b** showed a moderate anti-inflammatory activity.

It has been observed that the presence of the halogenated thiazole moiety decreased in all cases the anti-inflamatory activity (Table I, entries 3, 4, 9, 10), compared with the corresponding non-halogenated compounds (Table I, entries 2, 6, 7).

According to prevously reported data, the oxadiazole, thiadiazole and thiazole rings presented also, in this case, a potent anti-inflammatory activity. The triazole ring presented a non-significant anti-inflammatory activity.

Conclusions

In conclusion, the synthesis and physico-chemically characterisation of new polyheterocyclic thioethers was successfully achieved. The results of the evaluation of their anti-inflammatory activity revealed that three of the obtained compounds (**1a, 2f and 2h**) are promising candidates for the treatement of inflammation.

The structure – activity relationship evaluation revealed that not only the heterocyclic systems such as: oxadiazole, thiadiazole and 2-phenylthiazole, but also their reciprocal influence are responsible for the increasement of the anti-inflammatory activity.

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