

AN EVALUATION OF THE ANTI-INFLAMMATORY POTENTIAL OF SOME POLYHETEROCYCLIC COMPOUNDS WITH THIAZOLE RINGS IN ACUTE INFLAMMATION MODELS. PART I. VASCULAR RESPONSE

CRISTINA MOGOȘAN¹, OLIVIU VOȘTINARU^{1*}, ALINA ELENA PÂRVU², CRISTINA POP¹, VALENTIN ZAHARIA³

¹*Department of Pharmacology, Physiology and Physiopathology, Faculty of Pharmacy, University of Medicine and Pharmacy "Iuliu Hațieganu", RO-400012, Cluj-Napoca, Romania*

²*Department of Physiopathology, Faculty of Medicine, University of Medicine and Pharmacy "Iuliu Hațieganu", RO-400012, Cluj-Napoca, Romania*

³*Department of Organic Chemistry, Faculty of Pharmacy, University of Medicine and Pharmacy "Iuliu Hațieganu", RO-400012, Cluj-Napoca, Romania*

**corresponding author: oliviu_vostinaru@yahoo.com*

Abstract

The anti-inflammatory effect of some polyheterocyclic compounds with thiazole rings in acute inflammation models was evaluated following their influence on the vascular response within the inflammatory process. The compounds possess an anti-inflammatory effect as they may decrease the inflammatory oedema induced by 10% kaolin.

Rezumat

Efectul antiinflamator al unor derivați poliheterociclici cu nucleu tiazolic a fost evaluat într-un model de inflamație acută pentru a aprecia modul în care acești compuși influențează răspunsul vascular al procesului inflamator. Compușii au prezentat efect antiinflamator, deoarece au redus edemul inflamator indus de caolin 10%.

Keywords: thiazole, kaolin-induced oedema, vascular response, anti-inflammatory effect.

Introduction

Both the thiazole and the 1,2,4-triazole rings are well known for their pharmacological potential as they are found in molecules with the following properties: anti-infectious, antineoplastic, anticonvulsant, inhibition of platelet aggregation, antihistaminic, anti-inflammatory and many others. Furthermore, several precursors of the 1,2,4-triazols such as the acylthiosemicarbazides and the thiosemicarbazones also possess a series

of biological properties, either identical or different from their cyclization derivatives [3, 4, 7, 8].

The main purpose of this study has been the evaluation of the anti-inflammatory potential of certain thiazolyl-mercaptotriazole derivatives, their precursors (thiazolyl-thiosemicarbazones, thiazolyl-carbonil-thiosemicarbazides) as well as some thiazolo-triazole and pyrazole compounds that were obtained by the way of thiazolyl-mercaptotriazoles (Figure 1) in acute inflammation models in order to better assess how the studied compounds influence the vascular modifications in acute inflammation [9].

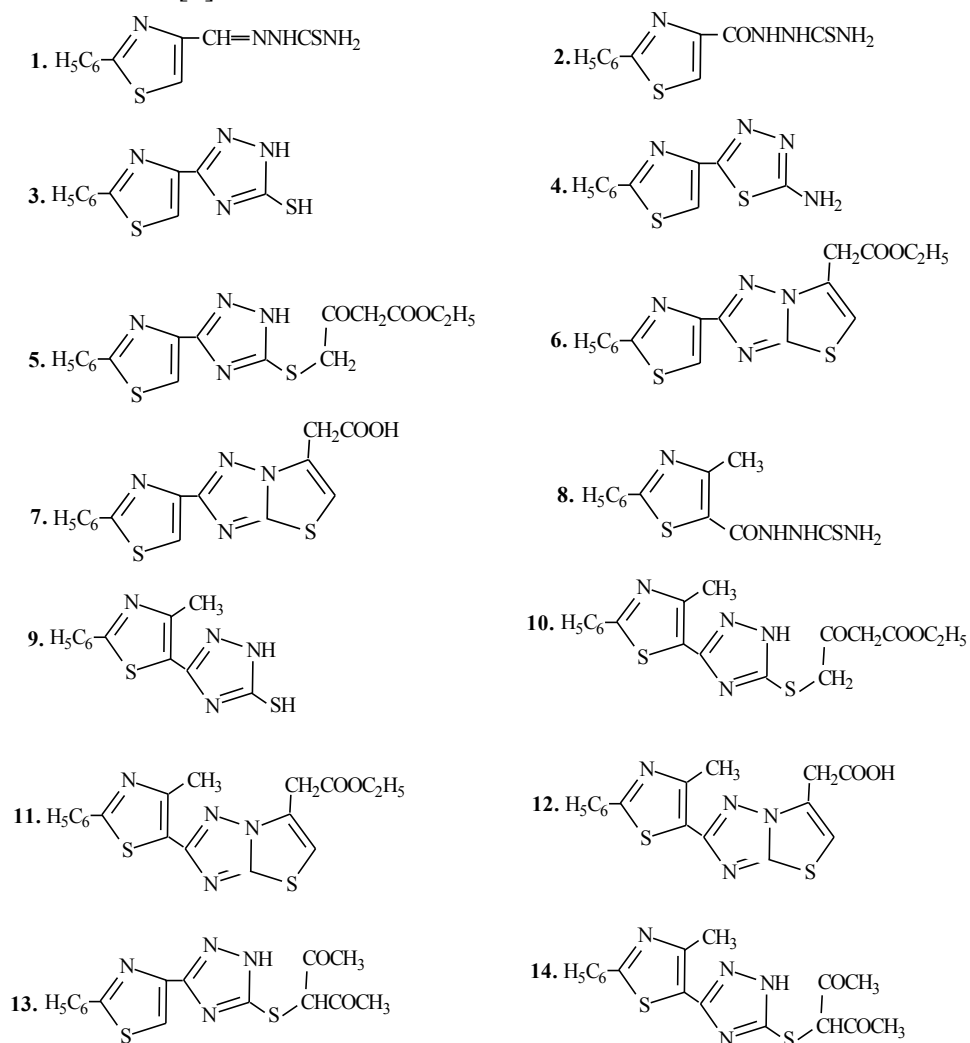


Figure 1a
The structures of the synthesized compounds

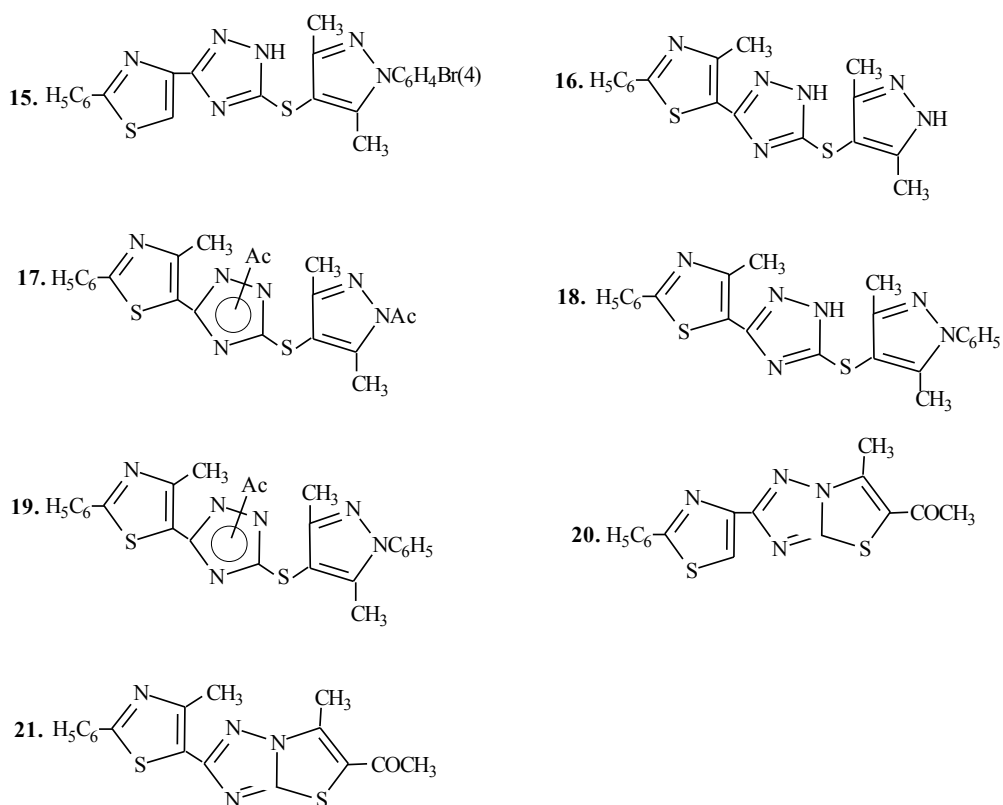


Figure 1b
The structures of the synthesized compounds

Materials and Methods

The first part of our study evaluated the anti-inflammatory potential of sixteen thiazole derivatives within the model of rat's paw oedema induced by 10% kaolin in order to assess how these compounds influence the vascular response within the acute inflammation [2].

The study was carried out using the modified method of Winter et al. [6]. Eighteen groups, each consisting of 10 male rats belonging to the Wistar Bratislava breed and weighing between 110-160g were used for this study. The rats were held in standard conditions, with *ad libitum* access to food and water. The studied substances were administered through intraperitoneal methods as follows:

- the first group– the control group (C); the vehicle used to prepare the suspensions (distilled water and Tween 80) was administered i.p. 1mL/animal
- the second group– the standard group (S); 50 mg/kg body weight of phenylbutazone suspension was administered i.p., 1mL of suspension/animal
- groups 3-18 – the tested groups; the tested substances were administered i.p as aqueous suspensions 40mg/kg body weight doses, 1 mL of suspension/animal. This dose used is taken from published studies with thiazole compounds [3, 4].

30 minutes after the substances were administered i.p., the volume of each animal's left back paw was measured plethysmographically with an Ugo Basile 7140 Plethysmograph. This represented the initial volume of the paw (V_0). Then the inflammation was induced by intra-plantar administration of 0.1 mL of 10% kaolin suspension in the measured paw. The evolution of the inflammatory oedema was closely followed by taking new measurements of the inflamed paw's volume two hours (V_2), 4 hours (V_4) and 24 (V_{24}) hours after the oedema was induced with kaolin. For each group the following calculations were made:

- the oedema's volume (E) at various time intervals ($E_2 = V_2 - V_0$ after 2 h; $E_4 = V_4 - V_0$ after 4 h, $E_{24} = V_{24} - V_0$ after 24 h)
- the standard error
- the percentage of oedema inhibition according to the formula:

$$\% \text{ inhibition of the inflammatory oedema} = (1 - X_t/X_c) \times 100,$$

where X_t represents the mean inflammatory oedema for the tested substances groups (in mL) and X_c is the mean inflammatory oedema of the control group (in mL) [1, 5].

The statistical analysis of the results was conducted by *t* Student testing ($p < 0.05$).

All experiments were performed according to the "Principles of Laboratory Animal Care" (NIH Publication No. 85; rev. 1985) and were approved by the Ethics Committee of the University Nr. 230/07.01.2011.

Results and Discussion

Table I shows the average values of the inflammatory oedema at various time intervals after the inflammation was induced by intra-plantar administration of 10% kaolin. Table II presents the percentage of oedema inhibition for the studied substances in the same experiment.

Table I

The values of the inflammatory oedema at various time intervals after the 10% kaolin induced inflammation ($p < 0.05$)

Tested group	Dose (mg/kg bw)	Oedema after 2 h (mL)	Oedema after 4 h (mL)	Oedema after 24 h (mL)
Vehicle (control)	-	0.69±0.04	0.79±0.10	1.13±0.18
Phenylbutazone (standard)	50	0.41±0.06*	0.51±0.18*	0.57±0.13*
1	40	0.63±0.16	0.59±0.25	1.61±0.31*
2	40	0.54±0.11*	0.57±0.09*	1.59±0.22*
3	40	0.74±0.19	0.67±0.17	1.55±0.13*
4	40	0.43±0.1*	0.55±0.08*	1.34±0.08
8	40	0.77±0.19	0.63±0.13	1.08±0.13
9	40	0.83±0.03*	0.59±0.08*	1.06±0.13
13	40	0.33±0.11*	0.39±0.10*	1.14±0.15
14	40	0.58±0.07	0.64±0.22	1.23±0.15
15	40	0.3±0.11*	0.33±0.1*	0.87±0.12*
16	40	0.35±0.12*	0.35±0.09*	0.86±0.12*
17	40	0.68±0.17	0.74±0.22	0.7±0.25*
18	40	0.87±0.24	0.92±0.26	0.96±0.14
19	40	0.73±0.2	0.71±0.33	0.67±0.34*
20	40	0.83±0.11	0.51±0.23*	0.42±0.16*
21	40	0.63±0.06	0.43±0.17*	1.11±0.10
22	40	0.73±0.13	0.67±0.13	1.11±0.09

Table II

Percentage of oedema inhibition at different time intervals after the 10% kaolin induced inflammation

Tested group	Dose (mg/kg bw)	% oedema inhibition after 2 h (mL)	% oedema inhibition after 4 h (mL)	% oedema inhibition after 24 h (mL)
Vehicle (control)	-	-	-	-
Phenylbutazone (standard)	50	40.57	35.44	49.55
1	40	8.69	25.31	-42.47
2	40	21.74	27.85	-40.70
3	40	-7.25	15.19	-37.17
4	40	37.68	30.37	-18.58
8	40	-11.59	20.25	4.42
9	40	-20.29	25.31	6.19
13	40	52.17	50.63	-0.88
14	40	15.94	18.99	-8.85
15	40	56.52	58.23	23.01
16	40	49.27	55.7	23.89
17	40	1.45	6.33	38.05
18	40	-26.09	-16.45	15.04
19	40	-5.80	10.13	29.20
20	40	-20.30	35.44	62.83
21	40	8.69	45.57	9.82
22	40	-5.80	15.19	1.77

Some of the substances managed to reduce the inflammatory oedema at various time intervals after it was induced by 10% kaolin.

Phenylbutazone, used as the reference anti-inflammatory substance, caused a significant decrease of the inflammatory oedema in all three measurement stages.

Two hours after the inflammation was induced, the left back paw oedema of the group we treated with compounds **2**, **4**, **13**, **15**, **16** was significantly smaller than the similar paw oedema of control group. Four hours after the induced inflammation, substances **2**, **4**, **9**, **13**, **15**, **16**, **20** and **21** caused significant decrease of the inflammatory oedema whereas 24 hours after the oedema was induced only substances **15**, **16**, **17**, **19** and **20** continued to diminish the inflammation.

When compared to phenylbutazone, compounds **4**, **13**, **15** and **16** had a similar or close response 2 hours after the induced inflammation, compounds **13**, **15**, **16** and **21** acted in a similar manner 4 hours afterwards, while compound **20** outpassed phenylbutazone in decreasing the inflammation 24 hours after it was induced. It is worth mentioning that substances **13**, **15** and **16** were able to reduce the inflammatory oedema at half the values of the control group and below the values obtained with phenylbutazone which was the reference anti-inflammatory substance.

Conclusions

The studied compounds proved an anti-inflammatory effect, thus influencing the vascular modifications in acute inflammation. Compounds **13**, **15**, **16** possess the best anti-inflammatory action. Except for compound **13**, they all have a pyrazole structure.

The differences concerning the anti-inflammatory effect among the studied substances come from the structural differences which can determine different physical and chemical properties, a different pharmacokinetic behavior, a greater or smaller selectivity for the receptor structure or even different mechanisms of action.

Acknowledgements

This work was supported by CNCSIS-UEFISCSU, project number PN II-IDEI code 1269-2008.

References

1. Ignat A, Zaharia V, Mogoşan C, Palibroda N, Cristea C, Silaghi-Dumitrescu L. Heterocycles 25. Microwave Assisted Synthesis of Some *p*-Toluensulfonyl-

- hydrazinothiazoles with Analgesic and Anti-Inflammatory Activity, *Farmacia* 2010, 58, 3:290-302
2. Kumakura S, Kamo I, Tsurufuji S. Role of bradikinin generating and degrading systems in the vascular permeability response induced with kaolin in rats, *Adv.Exp.Med.Biol.* 1989, 247 B:541-546
 3. Singhal N, Sharma PK, Dudhe R, Kumar N, Recent advancement of triazole derivatives and their biological significance. *J.Chem.Pharm.Res.* 2011, 3(2):126-133
 4. Siddiqui N, Arshad MF, Ahsan W, Alam MS. Thiazoles: A valuable Insight into the Recent Advances and Biological Activities. *IJPSDR* 2009, 1(3):136-143
 5. Vogel HG. Drug Discovery and Evaluation. Pharmacological Assays, Second Edition Ed. *Springer Verlag Berlin Heidelberg* 2002, 759-762
 6. Winter CA, Risley EA, Nuss GW. Carrageen-induced oedema in hind paw of the rats – an assay for anti-inflammatory drugs. *Proc. Soc. Exp. Biol. Med.* 1962, 111: 544-547.
 7. Zaharia V, Chirtoc I. Heterocycles 20. Synthesis and characterisation of 2-amino-5-(2-phenyl-4-methyl-thiazol-5-yl)-[1,3,4]-thiadiazole and 5-(2-phenyl-4-methyl-thiazol-5-yl)-[1,2,4]-triazol-[2H,4H]-3-thione, *Farmacia* 2002, L, 1: 38-43
 8. Zaharia V, Zaharia D, Chirtoc I, Palibroda N. Heterocycles 19. Synthesis and characterisation of 2-amino-5-(2-phenyl-thiazol-4-yl)-[1,3,4]-thiadiazole and 5-(2-phenyl-thiazol-4-yl)-[1,2,4]-triazol-[2H,4H]-thione, *Chujul Medical* 2002, LXXV, 4: 713-719
 9. Zaharia V, Silvestru A, Palibroda N, Mogoşan C. Heterocycles 28. Synthesis and Characterization of Some Bis and Polyheterocyclic Compounds with Anti-Inflammatory Potential, *Farmacia* 2011, 59, 5: 624-635.

Manuscript received: December 19th 2011