ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. XXII, N 2, 9, 2009 SECTIO DDD DOI: 10.2478/v10080-008-0180-0

Department of Organic Chemistry, Medical University of Lublin

EDYTA KUŚMIERZ, MONIKA WUJEC

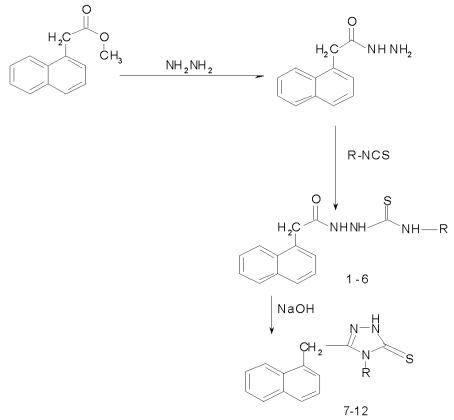
Synthesis of new derivatives of 4-substituted-3-(naphtalen-1-ylmethyl)-Δ²-1,2,4-triazoline-5-thiones

Synteza nowych pochodnych 4-podstawionych-3-(naftyl-1-ylometylo)-*Δ*²-1,2,4-triazolino-5-tionu

During the last few decades, much attention has been paid to the synthesis of 1,2,4-triazole derivatives which possess important pharmacological activities. Depending on the type of substituted groups, derivatives of 1,2,4-triazoline-5-thione show very different biological action: analgesic [6, 10], anti-inflammatory [7–9], bacteriostatic and antivirus properties [1, 3–5]. There are some antimicrobial drugs containing triazole moiety. For istance, fluconazole, vibunazole, alteconazole and itraconazole are used in medical therapy. In addition, Vorozole, Letrozole, Fadrozole and Anastrozole are nonsteroidal drugs for the treatment of estrogen dependent breast cancer [2].

RESULTS AND DISCUSSION

1-Naphtaleneacethydrazide was obtained from methyl-1-naphthalene acetate with hydrazine hydrate 80% and dry ethanol. The new thiosemicarbazide derivatives (1–6) were obtained in the reaction of hydrazide with isothiocyanates. These compounds were subjected to cyclization in 2% solution of sodium hydroxide, giving suitable 4-substituted-3-(naphtalen-1-ylmethyl)-Δ²-1,2,4-triazoline-5-thiones (7–12). The reactions were performed according to the Scheme (1). The cyclization of 4-benzoyl-1-(naphtalen-1-ylacetyl)thiosemicarbazide (6) in alkaline medium led to 3-(naphtalen-1-ylmethyl)-Δ²-1,2,4-triazoline-5-thione (12).



R= C_2H_5, C_6H_{11}, C_6H_5, 4-$CH_3OC_6H_4$, 2-FC_6H_4, COC_6H_5,

EXPERIMENTAL

All chemicals were purchased from Lancaster or Merck Co and used without purification. Melting points were determined in a Fisher-Johns block without corrections. The ^{1}H NMR spectra were recorded on a Brucke Avance 300 in DMSO-d_6 with TMS on internal standard. Elemental analyses were performed on a Perkin-Elmer analyzer and were in range of ± 0.40% for each element analyzed (C, H, N).

Naphtalen-1-ylmethyl-4-substituted thiosemicarbazides (1–6)

Hydrazide (1 g) and isothiocyanates (0.01 mol) were mixed and heated in oil bath at the 120–150°C for 4 h. The product was washed with diethyl ether to remove the unreacted isothiocyanate, dried and crystallized from 95% ethanol.

4-ethyl-1-(naphtalen-1-ylacetyl)thiosemicarbazide (1)

m.p. =189-191°C, Yield: 78%

Analysis for $C_{15}H_{17}N_3OS$ (287.38) – calcd: 62.69% C, 5.96% H, 14.62% N.
found: 62.46% C, 5.78% H, 14.46% N.

^{1}H NMR (DMSO-d_6 ppm): 1.04, 1.06, 1.09 (t, 3H, CH_3) *J*=7 Hz, 3.42, 3.44, 3.48, 3.51 (q, 2H, CH_2) *J*=7 Hz, 3.96 (s, 2H, CH_2), 7.44-7.94 (m, 7H, ar. naphthalene), 8.07-8.10 (m, 1H, NH), 9.26, 10.03 (2s, 2H, 2 NH).

4-cyclohexyl-1-(naphtalen-1-ylacetyl)thiosemicarbazide (2)

m.p. = 185-189°C, Yield: 81%

Analysis for $C_{19}H_{23}N_3OS$ (341.47) – calcd: 66.83% C, 6.79% H, 12.31% N.
found: 67.72% C, 6.64% H, 11.95% N.

^{1}H NMR (DMSO-d_6 ppm): 1.03-1.76 (m, 10H, cyclohexane), 3.95 (s, 2H, CH_2), 4.01 (s, 1H, cyclohexane), 7.40-8.13 (m, 7H, ar. naphthalene), 7.30, 9.18, 10.02 (3s, 3H, 3 NH).

4-phenyl-1-(naphtalen-1-ylacetyl)thiosemicarbazide (3)

m.p. = 168-174°C, Yield: 89%

Analysis for $C_{19}H_{17}N_3O_3S$ (335.42) – calcd: 68.04% C, 5.11% H, 12.53% N.
found: 67.87% C, 5.45% H, 12.82% N.

^{1}H NMR (DMSO-d_6 ppm): 4.03 (s, 2H, CH_2), 7.14-8.15 (m, 12H, ar. naphthalene and ar. benzene), 9.68, 10.29 (2s, 3H, 3 NH).

4-methoxyphenyl-1-(naphtalen-1-ylacetyl)thiosemicarbazide (4)

m.p. = 187-190°C, Yield: 83%

Analysis for $C_{20}H_{19}N_3O_2S$ (365.45) – calcd: 65.73% C, 5.24% H, 11.50% N.
found: 65.80% C, 5.34% H, 11.61% N.

^{1}H NMR (DMSO-d_6 ppm): 3.74 (s, 3H, CH_3), 4.02 (s, 2H, CH_2), 6.89, 6.90; 6.92, 6.93 (dd, 4H, ar. benzene) *J*=2 Hz, 7.42-8.38 (m, 7H, ar. naphthalene), 9.53, 9.57, 10.25 (3s, 3H, 3 NH).

4-(2-fluorophenyl)-1-(naphtalen-1-ylacetyl)thiosemicarbazide (5)

m.p. = 178-182°C, Yield: 82%

Analysis for $C_{19}H_{16}FN_3OS$ (353.41) – calcd: 64.57% C, 4.56% H, 11.89% N.
found: 64.26% C, 4.64% H, 11.53% N.

^{1}H NMR (DMSO-d_6 ppm): 4.01 (s, 2H, CH_2), 7.16-8.19 (m, 11H, ar. naphthalene and ar. benzene), 9.53, 9.82, 10.36 (3s, 3H, 3 NH).

4-benzoyl-1-(naphtalen-1-ylacetyl)thiosemicarbazide (6)

m.p. = 180-183°C, Yield: 73%

Analysis for $C_{20}H_{17}N_3O_2S$ (363.43) – calcd: 66.10% C, 4.71% H, 11.56% N.
found: 66.04% C, 4.51% H, 11.62% N.

^{1}H NMR (DMSO-d_6 ppm): 4.14 (s, 2H, CH_2), 7.43-8.19 (m, 12 H, ar. naphthalene and ar. benzene), 11.28, 11.71, 12.68 (3s, 3H, 3 NH).

4-substituted-3-(naphtalen-1-ylmethyl)-Δ^2-1,2,4-triazoline-5-thiones (7–12)

A mixture of thiosemicarbazide (**1-6)** (0.01 mole) and 50-60 cm^3 of 2% solution of sodium hydroxide was boiled for 2-3 h. After cooling the solutions was neutralized with dilute hydrochloric acid. The precipitate was filtered off and then crystallized from 95% ethanol.

4-ethyl-3-(naphtalen-1-ylmethyl)-Δ^2-1,2,4-triazoline-5-thione (7)

m.p. = 192-195^{o}C, Yield: 87%

Analysis for $C_{15}H_{15}N_3S$ (269.36) – calcd: 66.89% C, 5.61% H, 15.60% N.
found: 66.78% C, 5.56% H, 15.34% N.

^{1}H NMR (DMSO-d_6 ppm): 0.98, 1.01, 1.03 (t, 3H, CH_3) *J*=7 Hz, 3.94, 3.96, 3.99, 4.01 (q, 2H, CH_2) *J*=7 Hz, 4.58 (s, 2H, CH_2), 7.40-8.10 (m, 7H, ar. naphthalene), 13.53 (s, 1H, NH).

4-cyclohexyl-3-(naphtalen-1-ylmethyl)-Δ^2-1,2,4-triazoline-5-thione (8)

m.p. = 267-268^{o}C, Yield: 63%

Analysis for $C_{19}H_{21}N_3S$ (324.30) – calcd: 70.37% C, 6.53% H, 12.96% N.
found: 69.99% C, 6.83% H, 12.79% N.

^{1}H NMR (DMSO-d_6 ppm): 1.05-2.08 (m, 10H, cyclohexane), 4.20 (s, 1H, cyclohexane), 4.62 (s, 2H, CH_2), 7.27-8.06 (m, 7H, ar. naphthalene), 13.46 (s, 1H, NH).

4-phenyl-3-(naphtalen-1-ylmethyl)-Δ^2-1,2,4-triazoline-5-thione (9)

m.p. = 216-220^{o}C, Yield: 89%

Analysis for $C_{19}H_{15}N_3S$ (317.41) – calcd: 71.84% C, 4.76% H, 13.24% N.
found: 71.79% C, 4.61% H, 13.60% N.

^{1}H NMR (DMSO-d_6 ppm): 4.29 (s, 2H, CH_2), 6.98-7.96 (m, 12H, ar. naphthalene and ar. benzene), 13.76 (s, 1H, NH).

4-methoxyphenyl-3-(naphtalen-1-ylmethyl)-Δ^2-1,2,4-triazoline-5-thione (10)

m.p. = 233-235^{o}C, Yield: 67%

Analysis for $C_{20}H_{17}N_3OS$ (347.43) – calcd: 69.14% C, 4.93% H, 12.09% N.
found: 69.35% C, 4.88% H, 12.10% N.

^{1}H NMR (DMSO-d_6 ppm): 3.79 (s, 3H, CH_3), 4.27 (s, 2H, CH_2), 6.98, 6.99; 7.22, 7.23 (dd, 4H, ar. benzene) *J*=2 Hz, 7.01-7.93 (m, 7H, ar. naphthalene), 13.69 (s, 1H, NH).

4-[2-fluorophenyl-3-(naphtalen-1-ylmethyl)]- Δ^2-1,2,4-triazoline-5-thione (11)

m.p. = 289-293^{o}C, Yield: 76%

Analysis for $C_{19}H_{14}FN_3S$ (335.40) – calcd: 68.04% C, 4.21% H, 12.53% N.
found: 68.39% C, 4.60% H, 12.60% N.

^{1}H NMR (DMSO-d_6 ppm): 4.37 (s, 2H, CH_2), 7.04-8.29 (m, 11H, ar. naphthalene and ar. benzene), 13.89 (s, 1H, NH).

3-(naphtalen-1-ylmethyl)-Δ^2-1,2,4-triazoline-5-thione (12)

m.p. = 280-285^{o}C, Yield: 67%

Analysis for $C_{13}H_{11}N_3S$ (241.32) – calcd: 64.70% C, 4.59% H, 17.41% N.
found: 64.89% C, 4.61% H, 17.40% N.

^{1}H NMR (DMSO-d_6 ppm): 4.36 (s, 2H, CH_2), 7.41-8.09 (m, 7H, ar. naphthalene), 13.27 (s, 2H, 2 NH).

REFERENCES

1. Bhat A. R., Varadaraj Bhat G., Gautham Shenoy G.: Synthesis and *in-vitro* antimicrobial activity of new 1,2,4-triazoles, Journal of Pharmacy and Pharmacology, 53, 267, 2001.

2. Clemons M., Coleman R. E., Verma S.: Aromatase inhibitors in the adjuvant setting: bringing the gold to a standard? Cancer Treat. Rew., 30, 325, 2004.
3. Eweiss N. E., Bahajaj A. A., Elsherbini E. A.: Synthesis and antimicrobial activity of some 4-amino-5-aryl-1,2,4-triazole-3-thiones and their derivatives, J. Heterocycl. Chem., 23, 1451, 1986.
4. Johnson E. M., Szekely A., Warnock D.: *In vitro* Activity of Syn-2869, a Novel Triazole Agent, against Emerging and Less Common Mold Pathogens, Antimicrob. Agents Chemother., 43, 1260, 1999.
5. Mazzone G., Bonina F., Arrigo Reina R. et al.: Synthesis of 1-aroyl-4H (R)-thiosemicarbazides, the corresponding 5-aryl 4H (R)-1,2,4-triazoline-3-thiones and some derivatives of pharmaceutical interest, Farmaco, 36, 181, 1981.
6. Mekuskiene G., Gaidelis P., Vainilavicius P.: Synthesis and properties of 5-(4,6-diphenyl-2-pyrimidin-2-yl)-1,2,4-triazoline-5-thione and its derivatives, Pharmazie, 53, 94, 1998.
7. Sahin G., Palaska E., Kelicen P. et al.: Synthesis of some new 1-acylthiosemicarbazides, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and1,2,4-triazole-3-thiones and their anti-inflamatory activities, Arzneim. Forsch, 51, 478, 2001.
8. Schenone S., Bruno O., Ranise A. et al.: Synthesis and anti-inflammatory activity of esters derived from 5-aryl-1,2-dihydro-2-(2-hydroxyethyl)-3H-1,2,4-triazole-3-thiones, Farmaco, 53, 590, 1998.
9. Tozkoparan B., Gokhan N., Aktay G., Yesilada E.: 6-Benzylidenethiazolo[3,2-b]-1,2,4-triazole-5(6H)-ones substituted with ibuprofen: synthesis, characterization and evolution of anti-inflamtory activity, Eur. J. Med. Chem., 34, 743, 2000.
10. Turan-Zitouni G., Kaplancikli Z. A., Erol K., Killic F. S.: Synthesis andanalgesic activity of some triazoles and triazolothiadiazine, Il Farmaco, 54, 218, 1999.

SUMMARY

This paper is a continuation of studies on the cyclization of new acyl derivatives of thiosemicarbazide. In the reaction of 1-naphtaleneacethydrazide with isothiocyanates the respective thiosemicarbazides **(1–6)** were obtained. Further cyclization in alkaline medium led to the formation of 4-substituted-3-(naphtalen-1-ylmethyl)-Δ^2-1,2,4-triazoline-5-thiones **(7–12)** with promising pharmacological activity.

STRESZCZENIE

Praca jest kontynuacją badań nad cyklizacją nowych pochodnych tiosemikarbazydowych. W reakcji hydrazydu kwasu naftylo-1-octowego z izotiocyjanianami otrzymano odpowiednie tiosemikarbazydy **(1–6)**. Następnie cyklizacja w środowisku zasadowym prowadziła do otrzymania 4-podstawionych pochodnych 3-(naftyl-1-ylometylo)-1,2,4-triazolino-5-tionu **(7–12)** o spodziewanej aktywności farmakologicznej.