Dedicated to the memory of
acad. Ecaterina Cioranescu-Nenitzescu

New Heterocyclic Compounds with 1,3,4- Oxadiazole Structure

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In this paper, starting from 2–thiophenecarboxylic acid hydrazide a series of new 1,3,4-oxadiazole derivatives were synthesized and characterized. The 2–thiophenecarboxylic acid hydrazide was converted into N-(2-thenoyl)-N'-aroyl-hydrazine with different aromatic acids chloride in anhydrous pyridine medium. From the cyclization of N-(2-thenoyl)-N'-aroyl-hydrazine in the presence of $POCl_3$ resulted new 2-(2-thienil)-5-aryl-1,3,4-oxadiazoles. The structure of the synthesized compounds was confirmed by ^{1}H-NMR and ^{13}C-NMR spectral analysis.

Key Words: 1,3,4-oxadiazole derivatives, 2-thiophenecarboxylic acid hidrazide

In the last years, the condensed heterocyclic systems make up an interesting field, by the variety of the techniques synthesis and also by the biological properties which this compounds possess.

The synthesis of the 1,3,4-oxadiazole systems represents a very interesting field due to the different biological activities which these heterocycles have.

The literature presents different pharmacological action of this compounds: 2-R-amino-1,3,4-oxadiazoles substituted with aromatics radicals which have anti-inflamatory activity and those with halogen radical present analgesic activity [1], also the present literature presents many compounds with this structure which have possible aplication in antimicrobial therapy [2].

Many 1,3,4-oxadyazole compounds have bacteriostatic, antifungic, analgesic, hipoglycemiant action [3, 5] and some of them showed important activity against some types of human cancer [4].

The researches from 1,3,4-oxadyazole field makes us to consider that the best synthesis method is the cyclization of N-(2-thenoyl)-N'-aroyl-hydrazine in the presence of different agents ($POCl_3$, P_2O_5).

That is why, this paper presents the synthesis and characterization of some potential biological agents with 1,3,4-oxadiazole structure.

Experimental part

Materials and methods

The useful synthesis contains three stages:

The synthesis of acids chloride

In the first step of the synthesis, the different acids chloride (2) were obtained by treating, for three hours, the coresponding acids with thionyl chloride, according to the method presented in previous papers [6, 7, 8]. The mixture was refluxed for 3 h. The thionyl chloride in excess was removed by reduced pressure. For the next step, the acid chloride, was used in the crude status.

The synthesis of N-(2-thenoyl)-N'-aroyl-hydrazine

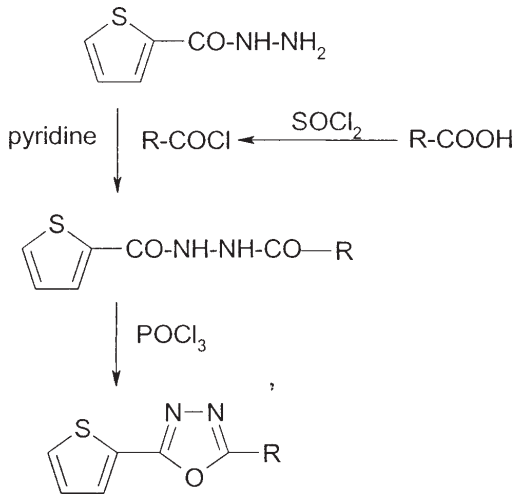
For the next step, a solution of 2–thiophenecarboxylic acid hydrazide and different acids chloride on a 1:1 molar raport, in anhydrous pyridine, is agitated (mixt up) for 2-3 h, at room temperature. The mixture obtained is poured over a cold and diluted HCl solution. The precipitate obtained is filtrated, washed with water and recristalised from different solvents.

The synthesis of 2-(2-thienil)-5-aryl-1,3,4-oxadyazoles

N-(2-thenoyl)-N'-aroyl-hydrazine (1 g) and 10 mL $POCl_3$ are placed in one round-bottom flask equipped with condenser and drying tube. The reaction mixture was refluxed, for 10-20 min, on small fire. The mixed up chilled on water jet and then poured on ice (without removing the $POCl_3$ by reduced pressure), gradually, under continous stirring and chilling to avoid the reaction mixture warming. The obtained precipitate is filtrated, washed with cold water and recristalised from different solvents.

All chemicals were obtained from commercial sources and used without further purification.

The reaction scheme is presented in the figure 1.



R= -C_6H_3 $(OMe)_2$ (2,4); -C_6H_3 $(OMe)_2$ (3,4); -C_6H_3 $(OMe)_2$ (3,5); -C_6H_3 $(OMe)_2$ (2,3); -C_6H_2 $(OMe)_2$ (3,4,5); -C_6H_3(4-Me, 3-NO_2) -$C_6H_3Cl_2$ (2,6)

Fig. 1. Synthesis of the new 1,3,4,-oxadiazole derivatives

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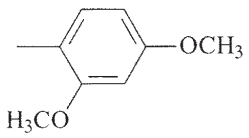
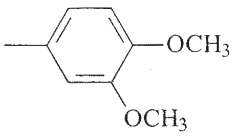
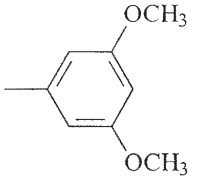
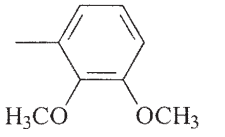
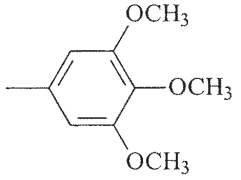
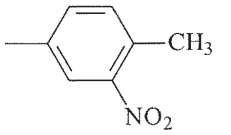
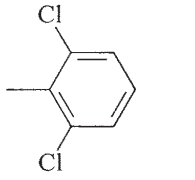
Table 1
THE NEW COMPOUNDS CHARACTERISTICS

No.	R	Molecular formula	Melting point (^{0}C)	Yield (%)
1		$C_{14}H_{12}SO_3N_2$	105^0-108^0 C	45
2		$C_{14}H_{12}SO_3N_2$	146^0-148^0 C	62
3		$C_{14}H_{12}SO_3N_2$	129^0-131^0 C	63
4		$C_{14}H_{12}SO_3N_2$	91^0-93^0 C	42
5		$C_{15}H_{14}SO_4N_2$	157^0-158^0 C	67
6		$C_{13}H_9SO_3N_3$	160^0-164^0 C	68
7		$C_{12}H_6SON_2Cl_2$	110^0-112^0 C	43

Results and discussions

The structure, molecular formula, molecular weight, melting point and the yield of the new 1,3,4-oxadiazole derivatives are given in the tabel 1.

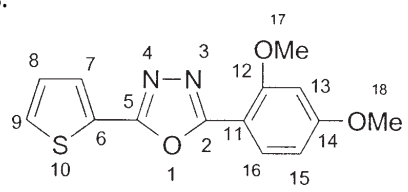
The new compounds are solid, crystallized, white or light yellow, soluble at normal temperature in DMSO and DMF and by heating in acetone, chloroform, benzene, toluene and xylene, insoluble in water.

All melting points were measured in glass capillary tubes on Electrothermal 9100 apparatus and are uncorrected.

Spectral data

The NMR spectra were recorded on a Gemini 300 BB (operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively) in DMSO-d6 using TMS as internal standard.

The spectral data confirmed the structure of obtained compounds.

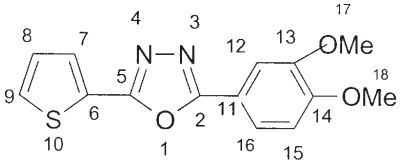


^{1}H-NMR(DMSO-d6, δ ppm, *J* Hz):

3.85 (s, 3H, H-17); 3.91 (s; 3H, H-18); 6.72 (dd, 2,3; 8.6, 1H, H-14); 6.75 (d, 2.3, 1H, H-12); 7.29 (dd, 3.7, 5.2, 1H, H-8); 7.83 (d, 8,6,1H, H-15); 7.81 (dd,1.2, 5.1, H-9); 7.91 (dd, 1.2, 3.7, 1H; H-7)

^{13}C – NMR(DMSO-d6, δ ppm):

55.69 (C-16(17)); 56.13 (C-17(16)); 99.10 (C-13); 104.66 (C-11); 106.32 (C-15) ; 124.62 (Cq-6); 128.75 (C-8); 130.01 (C-9); 131.21 (C-16) ; 131.35 (C-7); 159.11 (C-11(13)); 159.72 (C-13(11)); 162. 33 (C-2(5)) ; 163.68 (C-5(-2)).



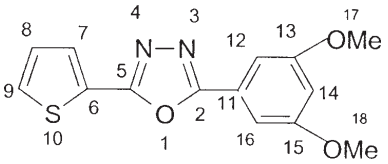
^{1}H-NMR(DMSO-d6, δ ppm, *J* Hz):

3.84 (s,3H, H-17(18)); 3.87 (s, 3H, H-18(17)); 7.16 (d, 8.4, 1H, H-15); 7.31 (dd,3.6, 5.1, H-8); 7.55 (d,1.9, H-12); 7.61 (dd,1.9, 8.4, 1H,H-16); 7.95 (m, 2H, H-7, H-9)

^{13}C-NMR(DMSO-d6, δ ppm):

55.78 (2C,C-17,C-18) ; 109.33 (C-12); 112.07 (C-15); 115.38 (Cq-11) ; 120.33 (C-16); 124.42 (Cq-6); 128.77

(C-8); 130.48 (C-7) ; 131.49 (C-9); 149.18 (C-13); 152.04 (C-14); 160.05 (C-2(5)) ; 163.56 (C-5(2)).

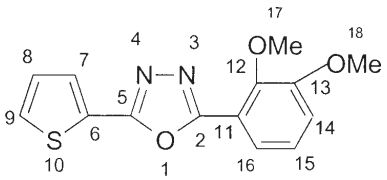


^{1}H-NMR(DMSO-d6, δ ppm, *J* Hz):

3.82 (s, 6H, H-17; H-18); 6.56 (t, 2.3, 1H, H-14); 7.14 (d, 2.3, 2H, H-12,16); 7.30 (dd, 3.8, 4.9, 1H, H-8); 7.92 (m, 2H, H-7, H-9)

^{13}C-NMR(DMSO-d6, δ ppm):

55.62 (C-17, C-18); 103.87 (C-14); 104.41 (C-12,C-16) ; 124.21 (Cq-6); 124.69 (Cq-11); 128.72 (C-8); 130.79 (C-7) ; 131.75 (C-9); 160.46 (C-2(6)); 160.99 (C-13;C-15); 163.28 (C-6(4).

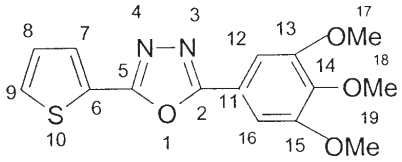


^{1}H-NMR (DMSO-d6, δ ppm, *J* Hz):

3.88 (s, 6H, H-17, H-18); 7.26 (t, 7.7, 1H, H-15); 7.31-7.50 (m, 2H, H-14, H-4); 7.50 (dd, 1.8, 7.7, 1H, H-16); 7.88 (dd, 1.5, 5.1,1H, H-9); 7.93 (dd, 1.5, 4.9, 1H, H-7)

^{13}C-NMR (DMSO-d6, δ ppm):

56.07 (C-17); 60.94 (C-18); 116.37 (C-14); 117.75 (Cq-11); 120.88 (CH-15); 124.33 (Cq-6); 125.03 (CH-16); 128.89 (CH-8); 130.42 (CH-7); 131.71 (CH-9); 147.26 (C-12); 153.50 (C-13); 160.49 (C-2(5)); 161.95 (C-5(4)).



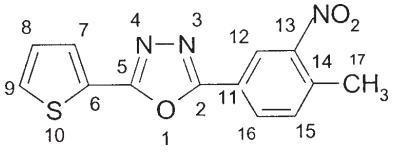
^{1}H-NMR (DMSO- d6,δ, ppm, JHz):

3.75 (s, 3H, H-17); 3.89 (s, 6H, H-16; H-18); 7.30 (dd, 3.6, 5.0, 1H, H-8); 7.32 (s, 2H, H-11, H-15); 7.93 (dd, 5.0, 1.1, 1H, H-5); 7.98 (dd, 1.1, 3.6, 1H, H-7)

^{13}C-NMR (DMSO-d6, δ ppm):

56.06 (C-17;C-19); 60.16 (C-18); 105.01 (C-12; C-16) ; 127.44 (Cq-2); 128.24 (C-4); 129.08 (C-3); 131.72 (C-9) ; 137.34 (Cq-6); 140.51 (Cq-13); 152.75 (C-13; C-15); 160.91 (C-9(7)) ; 165.31 (C-7(9)).

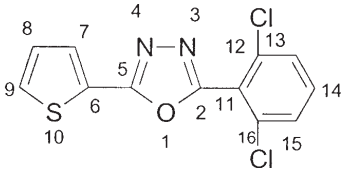
^{1}H-NMR (DMSO-d6, δ ppm, *J* Hz):



2.59 (s, 3H, H-17);7.34 (dd, 3.9, 4.9, H-8); 7.73 (d, 8.2, 1H, H-15); 8.01 (m, 2H, H-7, H-9); 8.24 (dd, 1.8, 8.2, 1H, H-16); 8.56 (d, 1.8, 1H, H-12)

^{13}C-NMR (DMSO-d6, δ ppm):

19.69 (C-17); 122.27 (C-12); 124.00 (Cq-11);128.88 (C_H-8); 130.70 (C_H-7); 131.09 (C_H-5);132.10 (C_H-15); 134.23



(C-16); 136.69 (Cq-6); 149.35 (Cq-13); 160.79 (C-6 (9)); 161.94 (C-9 (6))

^{1}H-NMR (DMSO-d6, δ ppm, *J* Hz):

8.05 (dd, 4.9, 1.0, 1H, H-9) ; 7.93 (dd, 3.8, 1.1, 1H, H-8) ; 7.75 (m, 3H, H-13, H-14, H-15) ; 7.31 (dd, 3.8, 4.9, 1H, H-7)

^{13}C-NMR (DMSO-d6, δ ppm,):

161.63 (C-11); 158.55 (C-8); 135.36 (C12, C16); 134.81 (C-7); 132.67 (CH); 131.41 (CH); 129.08 (C13, C15); 129.08 (C-14); 123.28 (C-11 (6)); 122.84 (C-6(11))

Conclusions

In order to synthesized new 1,3,4-oxadiazole derivatives with potential pharmacological activity, we obtained seven new 1,3,4-oxadiazole derivatives. The obtained compounds have been characterized by some physical properties.

The ^{1}H-NMR and ^{13}C-NMR spectral parameters confirm the structure of the prepared compounds. The biological activity of this compounds will be determinated and presented in the next papers.

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Manuscript received: 10.06.2009