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SYNTHESIS AND CHARACTERIZATION OF SOME BIOLOGICAL ACTIVE COMPOUNDS ON THE BASIS OF 2-THIOPHENE CARBOXYLIC ACID WITH HETEROCYCLIC AMINES

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The condensation reaction of 2-thenoil-isothiocyanate with heterocyclic amines, leads to new thioureides. For the new compounds synthesized from the 2-thiophenecarboxylic acid, the optimal reaction conditions to synthesized new thioureides with high purity and better yields we established. The new compounds were characterized by their physical properties (melting point, solubility) and through ^{1}H-NMR and ^{13}C-NMR spectroscopic analysis.

INTRODUCTION

Concerning the experience in synthesis of new thioureides [1-7] with potential pharmacological effects, we developed a new series of compounds (thioureides of 2-thiophenecarboxylic acid with heterocyclic amines), with the aim of obtaining compounds with potential pharmacological activity.

The biological activity of the complex with thiourea derivatives has been successfully screened for various biological actions: antidepressant, anticonvulsant, anthelmintic (nematodes), antihistaminic, anesthetic (local), antitussive, analgesic etc. [8-11]

In the literature is described a method for obtaining thioureides, which supposes the condensation of benzoyl-isothiocyanate with different amines. The new N-thenoyl-N'-(R-phenyl)-thioureides were obtained putting into practice the method used by G. J. Durant *et al.* [12] for the preparation of some benzoyl-thiourea derivatives.

Our new compounds were prepared by addition of some heterocyclic amines to 2-thenoil-isothiocyanate.

The synthesis of the new compounds was carried out in two steps.

The first stage was the synthesis of 2-thiophenecarboxylic chloride **(2)** by treating the 2-thiophenecarboxylic acid **(1)** with thionyl chloride, in anhydrous medium. The synthesis supposes an anhydrous medium, for the prevention of 2-thiophene acid chloride decomposition in the presence of water trace.

The acid chloride **(2)** was used for the next step of synthesis as crude material, after thionyl excess was removed by reduced pressure.

In the second stage of our synthesis the 2-thiophenecarboxylic acid chloride **(2)** was treated with ammonium thiocyanate (dried before 100ºC). The 2-thenoil-isothiocyanate **(3)** resulted after refluxing the reaction mixture for one hour in dry acetone.

The isothiocyanate was not isolated, the new thioureides **(4)** being obtained by adding the necessary amines. The reaction mixture was refluxed, under continuous stirring, for one hour.

The new substances were characterized by their physico-chemical properties and by ^{1}H-NMR and ^{13}C-NMR spectral analysis.

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EXPERIMENTAL

The ammonium thiocyanate was dried by heating at 100º C and the acetone using potassium carbonate. The liquid amines were dried using potassium hydroxide. The heterocyclic amines were Merck or Fulka products and they were not purified before use.

The synthesis of thiophene-2-carboxylic acid chloride:

In a round-bottom flask equipped with condenser and a drying tube were placed 5 g (0.039 mol) 2-thiophenecarboxylic acid and 91.72 g (56 mL) (0.77 mol) thionyl chloride. The mixture was refluxed for three hours. The thionyl chloride in exces was removed by reduced pressure.

The synthesis of the new thioureides (general procedure):

For the next step, a solution of 2-thiophenecarboxylic chloride (1g, 0.007 mol) in 6 mL anhydrous acetone was added to a solution of dry ammonium thiocyanate (0.53g, 0.007 mol) in 2 mL anhydrous acetone.

The reaction mixture was placed in one round-bottom flask equipped with condenser and drying tube. Then, it was refluxed with stirring one hour. After cooling, the corresponding heterocyclic amines (0.007 mol) in dry acetone (5 mL) was added in a small amounts, with stirring.

The mixture was refluxed for one hour.

Following cooling to ambient temperature, the mixture was poured into 500 mL water and the crude thioureide precipitates out. The purification was made through recrystallisation from isopropanol.

RESULTS AND DISCUSSION

The synthesis of the mentioned compounds is presented in Figure 1.

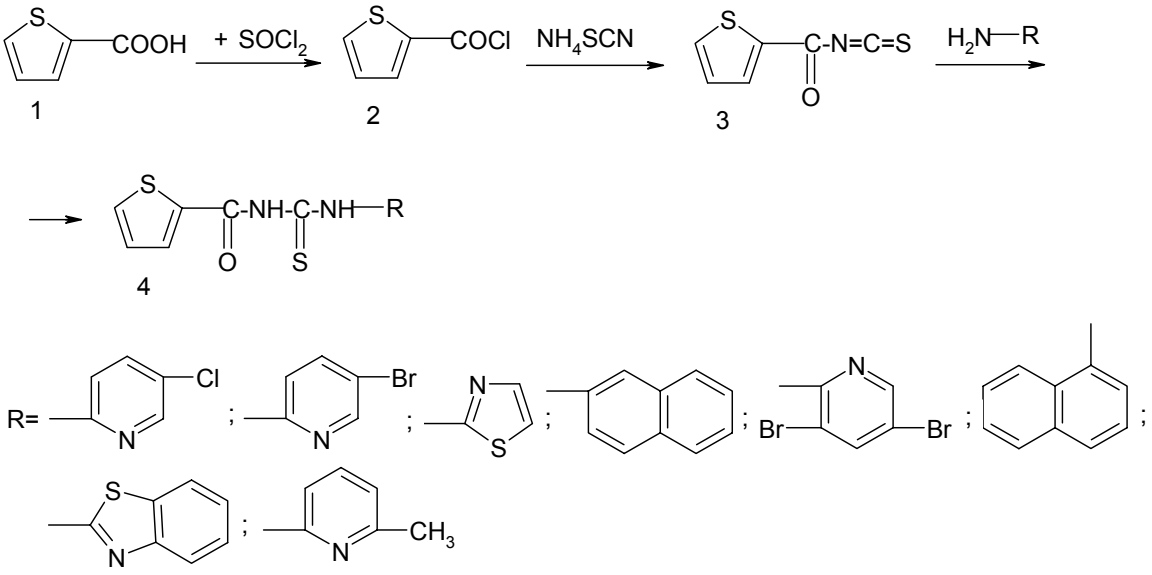


Fig. 1 –The synthesis of the new thioureides.

The structure, molecular formula, molecular weight, melting point and yield of the new thioureides are presented in Table 1.

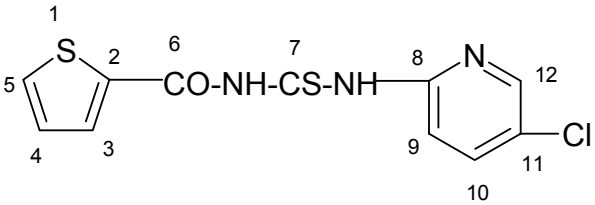
These novel compounds are well crystallized, having white or light-yellow colour; they are soluble at normal temperature in acetone and chloroform and by heating in inferior alcohols, benzene, toluene and xylene, insoluble in water and they have high melting points.

The melting points were measured in glass capillary tubes on Electrothermal 9100 apparatus, verified with a Boetius apparatus and are uncorrected.

Spectral data

The ^{1}H-RMN spectra were obtained at 300 MHz and the ^{13}C-RMN spectra were recorded at 75.075 MHz with a 300BB apparatus using solutions in DMSO-d6 as solvent and tetramethylsilane as internal standard.

The spectral data using ^{1}H-NMR and ^{13}C-NMR spectroscopy confirmed the structure of the obtained compounds.



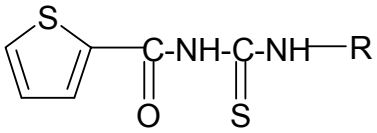
N-2-(5-chloropyridil)-N'-(2-thenoyl)-thiourea **(4a)**

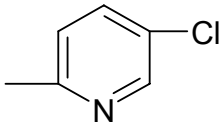
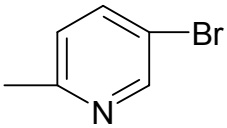
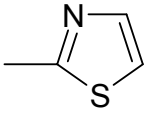
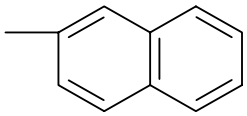
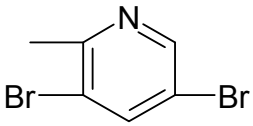
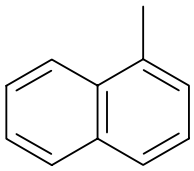
^{1}H-NMR (DMSO-d6, δppm, *J* Hz): 12.00 (sl, 2H,NH); 8.62 (sl, 1H-9); 8.48 (d, 2.6, 1H, H-12); 8.31 (dl, 1H, 1H-3); 8.05 (dl, 4.4, 1H, H-5); 8.00 (dd, 2.6, 8.9, 1H, H-10); 7.21 dd (3.1, 4,4, H-4)

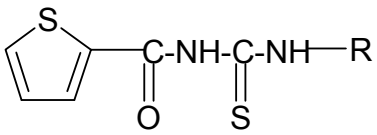
^{13}C-NMR (DMSO-d6, δppm): 178.46 (C-7); 162.58 (C-6); 150.56 (Cq); 147.29 (C-12); 140.42 (Cq); 138.49 (CH); 137.20 (CH); 136.13 (CH); 133.50 (CH); 129.40 (CH); 127.85 (Cq); 117.45 (CH)

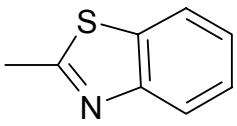
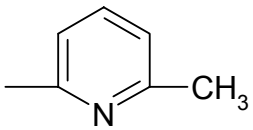
Table 1

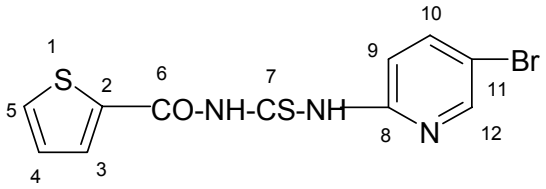
The new compounds characteristics



No.	R	Molecular formula	Molecular weight	Melting point (^{0}C)	Yield (%)
4a		$C_{11}H_8S_2ON_3Cl$	297.8	185.3-190.5 (isopropanol)	71
4b		$C_{11}H_8S_2ON_3Br$	342.2	186.7-190.3 (butanol)	64
4c		$C_9H_7S_3ON_3$	269.3	192.5-198.2 (isopropanol)	63
4d		$C_{16}H_{12}S_2ON_2$	312.4	149.4-152.4 (isopropanol)	60
4e		$C_{11}H_7S_2ON_3Br_2$	421.1	177.7-182.1 (butanol)	68
4f		$C_{16}H_{12}S_2ON_2$	312,4	171.6- 173.3 (isopropanol)	64



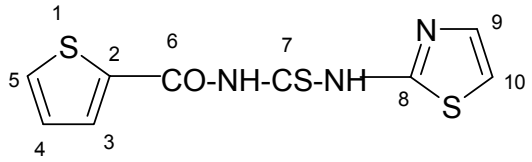
No.	R	Molecular formula	Molecular weight	Melting point (^{0}C)	Yield (%)
4g		$C_{13}H_9S_3ON_3$	319,4	184.4- 188.2 (isopropanol)	44
4h		$C_{12}H_{11}S_2ON_3$	277,3	162.2^0- 164.4^{0}C (isopropanol)	62



N-2-(5-bromopyridil)-N'-(2-thenoyl)-thiourea **(4b)**

^{1}H-NMR (DMSO-d6, δppm, *J* Hz): 8.58 (dl, 2.5, 1H, H-12); 8.32 (sl, 1H-9); 8.12 (dd, 2.5, 8.8, 1H, H-10); 8.08 (dd, 5.0, 1.0, H, H-5); 7.26 (dd, 5.0, 4.0, 1H, H-3)

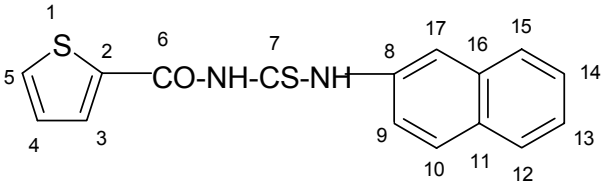
^{13}C-NMR (DMSO-d6, δ ppm): 177.55 (C-7); 162.01 (C-6); 150.1.7 (Cq); 148.85 (C-12); 140.61 (C-3); 135.50 (CH); 132.78 (CH); 128.77(CH); 116.99 (CH); 115.51 (C-11)



N-(2-thiazolyl)-N'-(2-thenoyl)-thiourea **(4c)**

^{1}H-NMR (DMSO-d6, δppm, *J* Hz): 8.31 (sl, 1H, H-3); 8.02 (dl, 3.8, H5); 7.21 (t, 4.1, H-4); 7.60 (d, 3.4, 1H, H-10); 7.25 (d, 3.4, 1H, H-9)

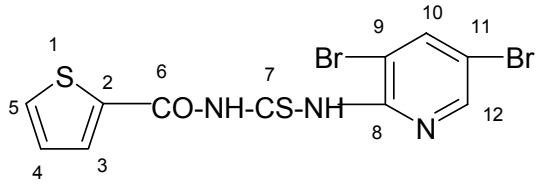
^{13}C-NMR (DMSO-d6, δ, ppm): 176.21 (C-7); 159.23 (Cq); 137.53 (CH); 135.28 (CH); 132.48 (CH); 128.63 (CH); 114.00 (CH)



N-(2-naphthyl)-N'-(2-thenoyl)-thiourea **(4d)**

^{1}H-NMR (DMSO-d6, δppm, *J* Hz): 12.9 (sl, 1H, NH); 11.55 (sl, 1H, NH); 8.38 (dd, 3.8, 1.1, 1H, H-3); 8.29 (d, 2.3, 1H, 1H, H-17); 8.03 (dd, 5.0, 1.1, 1H, H-5); 7.25 (dd, 5.0,3.8,1H, H-4); 7.93 (d, 8.5, 1H, H-10); 7.72 (dd, 8.5, 2.3, 1H, H-9); 7.90 (m, 2H, H-12, H-15); 7.52 (m, 2H, H-13, H-14)

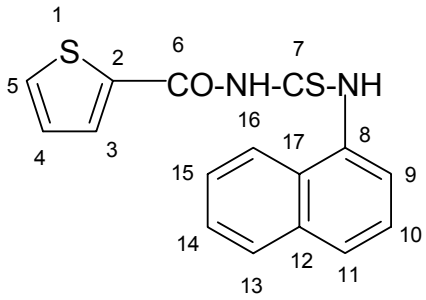
^{13}C-NMR (DMSO-d6, δppm): 179.72 (C-7); 162.84 (C-6); 137.28 (Cq); 136.34 (Cq); 135.95 (CH); 133.55 (CH); 133.45 (CH); 132.05 (Cq); 129.40(CH); 128.86 (CH); 128.40 (CH); 128.24 (CH); 127.27 (CH); 126.75(CH); 124.45(CH); 122.29 (CH)



N-2-(3,5-dibromopyridlil)-N'-(2-thenoyl)-thiourea **(4e)**

^{1}H-NMR (DMSO-d6, δ ppm, *J* Hz): 12.10 (sl, 1H, NH); 8.39 (dl, 3.9, 1H, H-3); 8.05 (dl, 4.3, 1H, H-5); 7.24 (dd, 4.3, 3.9, H-4); 8.65 (d, 2.2, 1H, H-12); 8.54 (d, 2.2, 1H, H-10)

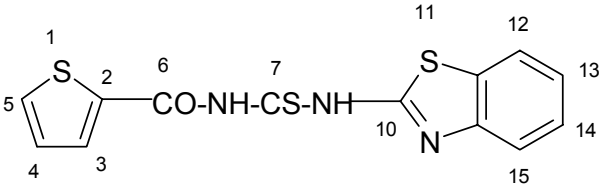
^{13}C-NMR (DMSO-d6, δ ppm): 179.77 (C-7); 161.55 (C-6); 148.76 (Cq-8); 148.16 (CH-12); 143.29 (CH-10); 136.17 (Cq); 135.31 (CH-3); 132.69 (CH); 128.53 (CH); 119.37 (Cq-9); 118.30 (Cq-11)



N-(1-naphthyl)-N'-(2-thenoyl)-thiourea **(4f)**

^{1}H-NMR (DMSO-d6, δppm, *J* Hz): 12.50 (sl, 1H, NH); 11.65 (sl, 1H, NH); 8.48 (dl, 3.7, 1H, H-3); 8.09 (dl, 5.0, 1H, H-5); 7.31 (dd, 5.0, 3.7, 1H, H-4); 7.60-8.05 (m, 7H, H-9, 10, 11, 13, 14, 15, 16)

^{13}C-NMR (DMSO-d6, δppm): 181.73 (C-7); 163.28 (C-6); 137.66 (Cq); 136.28 (CH-5); 135.17 (Cq); 134.72 (Cq); 133.77 (CH); 129.73 (CH); 129.65 (Cq); 129.33 (CH); 128.39 (CH); 127.73 (CH); 127.31 (CH); 126.43 (CH); 125.63 (CH); 123.15 (CH)

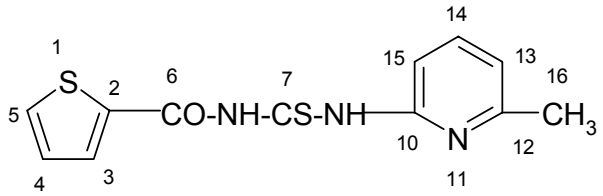


N-(2-benzothiazolyl)-N'-(2-thenoyl)-thiourea **(4g)**

^{1}H-NMR (DMSO-d6, δ ppm, *J* Hz): 12.30 (sl, 2H, H-7, H-9); 8.41 (dd, 3.9, 1.1, 1 H, H-3); 8.11 (dd, 4.9, 1.1, 1H, H-5); 8.08 (dl, 8.0, 1H, H-15); 7.81 (dd, 8.0, 1.4, 1H, H-12); 7.50 (td, 1.4, 8.0, 1H,

H-14 (13)); 7.40 (td, 1.2, 8.0, 1H, H-13 (14)); 7.30 (dd, 3.9, 4.9, 1H, H-4)

^{13}C-NMR (DMSO-d6, δppm): 178.42 (C-8); 167.69 (Cq); 163.36 (Cq); 136.93 (CH); 134.28 (CH); 129.76 (CH); 127.58 (CH); 125.44 (CH); 122.85 (CH); 126.61 (CH); 158.24 (Cq); 160.32 (Cq)



N-2-(6-methylpyridlil)-N'-(2-thenoyl)-thiourea **(4h)**

^{1}H-NMR (DMSO-d6, δ ppm, *J* Hz): 2.45 (s, 3H, CH3, H-16); 7.10 (d, 7.6, 1H, H-13); 7.23 (dd, 3.9, 5.0, 1H, H-4); 7.74 (t, 7.6, 1H, H-14); 8.00 (dd, 1.1, 5.0, 1H, H-5); 8.21 (m, 2H, H-3, H-15); 12.00 (sl, 2H, H-7, H-9)

^{13}C-NMR (DMSO-d6, δppm): 24.21 (C-16); 113.04 (C-3); 120.97 (CH-14); 129.16 (CH); 133.05 (CH); 135.62 (CH); 139.13 (CH); 151.56 (Cq); 157.48 (Cq); 161.57 (C-6); 178.14 (C-8); 162.9 (Cq)

CONCLUSION

We synthesized eight new thoiureides of 2-thiophenecarboxilic acid and the ^{1}H-NMR and ^{13}C-NMR spectral measurements confirmed the chemical structures of the synthesized compounds. The synthesis of the novel thioureides was completed through the condensation of 2-thenoil-isothiocyanates with different heterocyclic amines in anhydrous acetone.

The obtained compounds have been characterized by some physical properties. Starting from the ^{1}H-NMR and ^{13}C-NMR spectra, the structural formula of the new thioureides, deducted from the synthesis equations, were confirmed.

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