Dedicated to Prof. Gheorghi]a Jinescu on the occassion of her 70th birthday

Studies on Synthesis of Some Novel Thioureides of 2-(4-Methyl-phenoxymethyl)benzoic Acid with Antimicrobial Activity

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Thioureides of 2-(4-methyl-phenoxymethyl)benzoic acid have been synthesised by reaction of 2-(4-methyl-phenoxymethyl)benzoyl isothiocyanate with primary aromatic amines. The mentionated isothiocyanate was obtained in the reaction of the 2-(4-methyl-phenoxymethyl)benzoic acid chloride with ammonium thiocyanate. The acid chloride was prepared by reacting the coresponding acid, the 2-(4-methyl-phenoxymethyl)benzoic acid, with thionyl chloride and the aforementioned acid from potassium para-cresolate with phtalide. The reaction conditions were established to ensure the best yields. These new thioureides have been characterized by means of elemental analysis, IR and NMR spectral studies.

Keywords: thioureides, 2-(4-methyl-phenoxymethyl)benzoic acid, ^{1}H-NMR, ^{13}C-NMR

Thiourea and its derivatives such as thioureides, possess some interesting biological properties such as antibacterial, antifungal, antitubercular, antimalarial, antiviral, antineoplastic, antihelmintic etc. The remarkable pharmacological importance of N-acylated compounds was the main reason for choosing this theme of our research.

In previous papers we presented the synthesis and the structural confirmation of some thioureides of the 2-phenoxymethylbenzoic acid, 2-(4-methyl-phenoxy-methyl)benzoic acid, 2-(4-methoxy-phenoxymethyl) benzoic acid, 2-(4-chloro-phenoxymethyl)benzoic acid and some complex combinations of transitional metals with this thioureides [1-7].

Experimental part

All melting points were recorded with an Electrothermal 9100 apparatus and are uncorrected. Elemental analysis was realized using a Perkin Elmer CHNS/O Analyser Series II 2400 apparatus.

The NMR spectra were recorded on a Gemini 300BB instrument, at room temperature, operating at 300MHz for ^{1}H and 75MHz for ^{13}C and Unity Inova 400 instrument, operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. The new thioureides were dissolved in DMSO-d_6 and the chemical shifts were recorded as δ values in parts per million (ppm) relative with tetramethylsilane used as internal standard.

The IR spectra were performed with FT-IR Bruker Vertex 70 apparatus.

In a previous article [8] we presented the first and the second stage of the new thioureides synthesis: the synthesis of 2-(4-methyl-phenoxymethyl)benzoic acid and 2-(4-methyl-phenoxymethyl)benzoyl chloride.

The synthesis of the new thioureides (general procedure)

To a solution of ammonium thiocyanate (0.76 g, 0.01 mol) (mol. Wt. 76.13) in 5 mL dry acetone was added a solution of 2-(4-methyl-phenoxymethyl)benzoyl chloride (0.01 mol)(mol. Wt. 260.70) (0.01 mol) in 15 mL dry acetone. The acetone was dried over potassium carbonate and the ammonium thiocyanate by heating at 100^{0}C. The reaction mixture was refluxed one hour in a one round-bottom flask with condenser and a drying tube. After cooling, 0.01 mol of dry and freshly distilled primary aromatic amine in 2 mL dry acetone was added by stirring, to the reaction mixture. The mixture was then refluxed for one hour. The product was precipitated after the cooled reaction mixture was poured into 500 mL water.

The crude thioureides obtained were crystallised from isopropanol with active carbon.

Results and Discussion

The new compounds (**1**) were prepared by refluxing the 2-(4-methyl-phenoxymethyl)benzoyl isothiocyanate (**2**) with primary aromatic amines in dry acetone, knowing the high reactivity of isothiocyanates in the presence of the dry amines. The necessary liquid amines were dried with potassium hydroxide and afterwards distilled.

Isothiocyanate (**2**) was obtained by reaction between 2-(4-methyl-phenoxymethyl)benzoyl chloride (**3**) with ammonium thiocyanate in dry acetone. For the next step of synthesis, the isothiocyanate was not isolated and the necessary amines were directly added to the reaction mixture to give the thioureides.

The acide chloride was prepared by refluxing the 2-(4-methyl-phenoxymethyl)benzoic acid (**4**) with thionyl chloride, using anhydrous 1,2-dichloroethane as reaction medium.

The acid (**4**) was synthetized with the best yield using phtalide (**5**) which was treated with potassium *para*-cresolate in xylene under reflux. This gives the potassium salt (**6**) of 2-(4-methyl-phenoxymethyl)benzoic acid, which has good solibility in 10% aqueous sodium hydroxide solution, allowing its facile separation from xylene. The acid (**4**) then precipitated using a mineral acid solution.

The necessary potassium *para*-cresolate was obtained from the corresponding phenol and potassium hydroxide in xylene. The resulting water was removed by azeotropic distillation.

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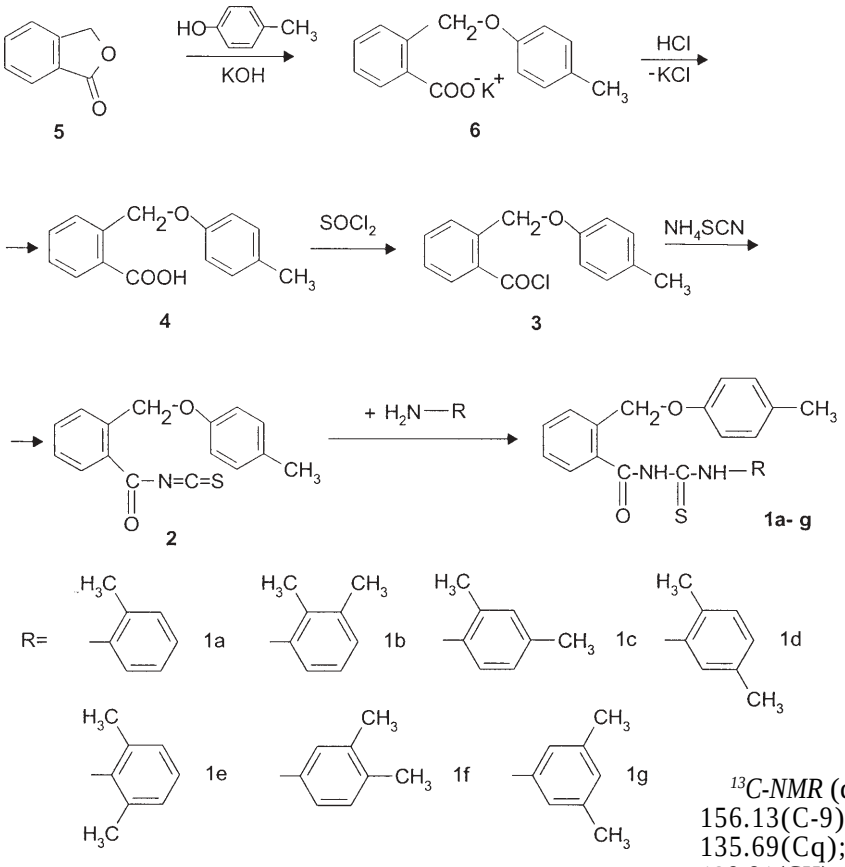


Scheme 1
The general scheme of synthesis

The reactions are presented in scheme 1.

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

The structure, elemental analysis, melting point and yield of the new thioureides are presented in Table 1.

The calculated formula provided by the elemental analysis results (table 1) is in good agreement with the expected structures.

Spectral data

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(2-methyl-phenyl)-thiourea

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 12.14(s, 1H, NH); 11.89(s, 1H, NH); 7.62(dd, 1H, H-7, 1.2, 7.5); 7.57(td, 1H, H-5, 7.5, 1.2); 7.52(d, 1H, H-4, 1.0, 7.5); 7.47(td, 1H, H-6, 1.0, 7.5); 7.07(d, 2H, H-11-13, 8.4); 6.88(d, 2H, H-10-14, 8.4); 5.26(s, 2H, H-8); 2.22(s, 3H, H-15); 2.14(s, 3H, H-23).

^{13}C-NMR (dmso-d6, δ ppm): 179.89(C-16); 170.29(C-1); 156.16(C-9); 141.19(Cq); 136.83(Cq); 135.73(Cq); 133.54(Cq); 133.33(Cq); 130.97(CH); 130.41(CH); 129.83(C-11-13); 129.72(CH); 128.55(CH); 127.84(CH); 127.02(CH); 126.51(CH); 114.57(C-10-14); 67.61(C-8); 20.11(C-15); 17.49(C-23-24).

FT-IR (ATR in solid, ν cm^{-1}): 3143m; 3024m; 2914w; 1674m; 1584w; 1507vs; 1385m; 1240s; 1156s; 1072w; 1019m; 945w; 870w; 814w; 730m; 656w; 610w; 513w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(2,3-dimethyl-phenyl)-thiourea

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 12.07(s, 1H, NH); 11.85(s, 1H, NH); 7.63(dd, 1H, H-7, 1.1, 7.2); 7.59(dd, 1H, H-4, 1.4, 7.2); 7.56(td, 1H, H-5, 1.2, 7.2); 7.47(td, 1H, H-6, 1.4, 7.2); 7.21(t, 1H, H-21, 6.7); 7.14÷7.11(m, 2H, H-20, H-22); 7.15(t, 1H, H-20, sist. A_2B, 4.7); 7.08(d, 2H, H-11-13, 8.6); 6.88(d, 2H, H-10-14, 8.6); 5.26(s, 2H, H-8); 2.26(s, 3H, H-15); 2.23(s, 3H, H-23 or H-24); 2.03(s, 3H, H-23 or H-24).

^{13}C-NMR (dmso-d6, δ ppm): 180.25(C-16); 170.28(C-1); 156.13(C-9); 137.19(Cq); 136.69(Cq); 135.70(Cq); 135.69(Cq); 133.53(Cq); 132.36(Cq); 130.91(CH); 129.81(CH); 129.80(C-11-13); 129.70(CH); 128.50(CH); 127.79(CH); 125.36(CH); 124.70(CH); 114.56(C-10-14); 67.58(C-8); 20.08(C-15); 19.97(C-23 or C-24); 13.80(C-23 or C-24).

FT-IR (ATR in solid, ν cm^{-1}): 3213w; 3128w; 3029w; 2920w; 1670m; 1578w; 1503vs; 1379m; 1331m; 1225s; 1147s; 1054m; 1026w; 953w; 880w; 827w; 733m; 674w; 640w; 511w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(2,4-dimethyl-phenyl)-thiourea

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 12.04(sl, 1H, NH); 11.81(sl, 1H, NH); 7.62(dd, 1H, H-7, 1.4, 7.3); 7.59(dd, 1H, H-4, 2.1, 7.3); 7.55(td, 1H, H-5, 1.4, 7.3); 7.46(td, 1H, H-6, 2.1, 7.3); 7.36(t, 1H, H-21, 7.8); 7.07÷7.00(m, 4H, H-11-13, H-19, H-22); 6.86(d, 2H, H-10-14, 8.6); 5.23(s, 2H, H-8); 2.26(s, 3H, H-23 or H-24); 2.20(s, 3H, H-15); 2.08(s, 3H, H-24 or H-23).

^{13}C-NMR(dmso-d6, δ ppm): 180.00(C-16); 170.34(C-1); 156.21(C-9); 136.41(Cq); 135.72(Cq); 134.26(Cq); 133.60(Cq); 133.12(Cq); 133.07(Cq); 131.00(CH); 130.99(CH); 129.89(C-11-13); 128.71(CH); 128.52(CH); 127.96(CH); 126.70(CH); 126.36(CH); 114.67(C-10-14); 67.76(C-8); 20.63(C-24); 20.14(C-15); 17.43(C-23).

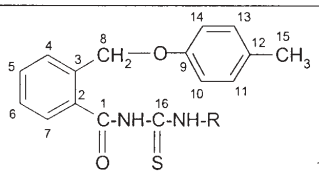
FT-IR (ATR in solid, ν cm^{-1}): 3230m; 3050m; 2912w; 1663m; 1592m; 1527vs; 1353m; 1224s; 1160s; 1115m; 1078w; 1012m; 954w; 875w; 812m; 739m; 657w; 613w; 509w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(2,5-dimethyl-phenyl)-thiourea

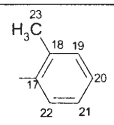
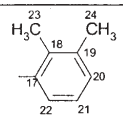
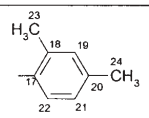
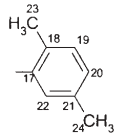
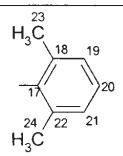
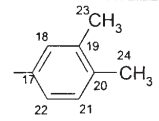
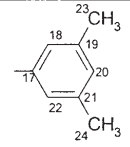
^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 12.08(s, 1H, NH); 11.86(s, 1H, NH); 7.62(dd, 1H, H-7, 1.4, 7.3); 7.59(dd, 1H, H-4, 2.1, 7.3); 7.55(td, 1H, H-5, 1.4, 7.3); 7.46(td, 1H, H-6, 2.1, 7.3); 7.27(d, 1H, H-22, 1.0); 7.15(d, 1H, H-19, 7.6); 7.07(d, 2H, H-11-13, 8.6); 7.02(dd, 1H, H-20, 1.0, 7.6); 6.88(d, 2H, H-10-14, 8.6); 5.25(s, 2H, H-8); 2.27(s, 3H, H-23 or H-24); 2.22(s, 3H, H-15); 2.10(s, 3H, H-23 or H-24).

Table 1

DATA ON THE NEW THIOUREIDES 1a-g



1a- g

Nr. crt.	R	C%		H%		N%		S%		Melting point (^{0}C)	Yield (%)
		c.	e.	c.	e.	c.	e.	c.	e.		
1a.		70.74	70.61	5.68	5.75	7.18	7.21	8.21	8.34	139,1-142	78
1b.		71.26	71.47	5.98	5.83	6.93	6.98	7.93	7.88	136,7-141,2	68
1c.		71.26	70.95	5.98	6.09	6.93	6.93	7.93	8.21	123,4- 126,1	73
1d.		71.26	70.89	5.98	5.85	6.93	6.89	7.93	7.98	161,2- 162,1	66
1e.		71.26	71.11	5.98	6.20	6.93	7.13	7.93	8.24	191,3- 194,1	72
1f.		71.26	71.39	5.98	5.87	6.93	6.91	7.93	7.80	128,2- 130,8	76
1g.		71.26	71.09	5.98	6.05	6.93	6.81	7.93	7.87	175,4- 178,3	64

where: c = calculated, e = experimental

^{13}C-NMR (dmso-d6, δ ppm): 179.83(C-16); 170.31(C-1); 156.15(C-9); 136.55(Cq); 135.64(Cq); 135.19(Cq); 133.57(Cq); 130.29(Cq); 129.65(Cq); 130.88(CH); 130.19(CH); 129.80(C-11-13); 128.55(CH); 128.45(CH); 127.81(CH); 127.68(CH); 126.85(CH); 114.53(C-10-14); 67.61(C-8); 20.48(C-23 or C-24); 20.07(C-15); 17.06(C-23 or C-24).

FT-IR (ATR in solid, ν cm^{-1}): 3151w; 3027w; 2919w; 1678m; 1583w; 1508vs; 1383w; 1334m; 1293w; 1237s; 1146s; 1072m; 1019w; 954w; 863w; 814w; 741m; 696w; 656w; 615w; 540w; 510w; 437w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(2,6-dimethyl-phenyl)-thiourea

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 11.86(sl, 1H, NH); 11.74(sl, 1H, NH); 7.63(dd, 1H, H-7, 1.2, 7.0); 7.59(dd, 1H, H-4, 1.4, 7.0); 7.56(td, 1H, H-5, 1.2, 7.0); 7.47(td, 1H, H-6, 1.4, 7.0); 7.15(t, 1H, H-20, sist. A_2B, 4.7); 7.11(d, 2H, H-19-21, sist. A_2B, 3.8); 7.07(d, 2H, H-11-13, 8.6); 6.88(d, 2H, H-10-14, 8.6); 5.26(s, 2H, H-8); 2.23(s, 3H, H-15); 2.19(s, 6H, H-23-24).

^{13}C-NMR (dmso-d6,δ ppm): 180.11(C-16); 169.92(C-1); 156.05(C-9); 136.03(Cq); 135.55(Cq); 135.02(C-18-22); 133.58(Cq); 129.60(Cq); 130.84(CH); 129.71(C-11-13); 128.70(CH); 128.47(CH); 127.76(CH); 127.75(CH); 127.30(CH); 114.55(C-10-14); 67.55(C-8); 20.02(C-15); 17.69(C-23-24).

FT-IR (ATR in solid, ν cm^{-1}): 3163s; 3023m; 2868w; 2831w; 1685m; 1505vs; 1383w; 1331w; 1291w; 1229m; 1159m; 1075w; 1031m; 947w; 877w; 826w; 803w; 748m; 683w; 654w; 615w; 553w; 521w; 438w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(3,4-dimethyl-phenyl)-thiourea

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 12.35(s, 1H, NH); 11.78(s, 1H, NH); 7.62(dd, 1H, H-7, 1.4, 7.3); 7.59(dd, 1H, H-4, 2.1, 7.3); 7.55(td, 1H, H-5, 1.4, 7.3); 7.46(td, 1H, H-6, 2.1, 7.3); 7.36(dd, 1H, H-22, 1.4, 7.8); 7.27(d, 1H, H-18, 7.8);

7.15(d, 1H, H-21, 7.8); 7.06(d, 2H, H-11-13, 8.0); 6.88(d, 2H, H-10-14, 8.6); 5.26(s, 2H, H-8); 2.22(s, 9H, H-15, H-23, H-24).

^{13}C-NMR (dmso-d6, δ ppm): 178.72(C-16); 170.12(C-1); 156.09(C-9); 136.45(Cq); 135.71(Cq); 135.45(Cq); 134.32(Cq); 133.31(Cq); 129.61(Cq); 130.09(CH); 129.74(C-11-13); 129.41(CH); 128.39(CH); 128.30(CH); 127.65(CH); 125.07(CH); 121.50(CH); 114.57(C-10-14); 67.51(C-8); 20.07(C-15); 19.27(C-23 or C-24); 18.83(C-23 or C-24).

FT-IR (ATR in solid, ν cm^{-1}): 3174m; 3030w; 2915w; 2856w; 1670m; 1583w; 1531vs; 1505vs; 1381w; 1332w; 1292w; 1236m; 1156m; 1029m; 901w; 810w; 729m; 693w; 668w; 607w; 561w; 511w; 422w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(3,5-dimethyl-phenyl)-thiourea

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 12.34(s, 1H, NH); 11.80(s, 1H, NH); 7.62(dd, 1H, H-7, 1.4, 7.3); 7.59(dd, 1H, H-4, 2.1, 7.3); 7.55(td, 1H, H-5, 1.4, 7.3); 7.46(td, 1H, H-6, 2.1, 7.3); 7.19(d, 2H, H-18-22, 0.9); 7.06(d, 2H, H-11-13, 8.6); 6.90(t, 1H, H-20, 0.9); 6.86(d, 2H, H-10-14, 8.6); 5.25(s, 2H, H-8); 2.27(s, 6H, H-23 and H-24); 2.21(s, 3H, H-15).

^{13}C-NMR (dmso-d6, δ ppm): 178.81(C-16); 170.34(C-1); 156.20(C-9); 137.86(C-19-20); 137.71(Cq); 135.82(Cq); 133.43(Cq); 129.69(Cq); 128.43(CH); 129.87(C-11-13); 131.01(CH); 128.52(CH); 127.80(CH); 121.81(CH); 114.61(C-10-14); 67.59(C-8); 20.89(C-23-24); 20.13(C-15).

*FT-IR (*ATR in solid, ν cm^{-1}): 3150m; 3022w; 2911w; 2866w; 1673m; 1506vs; 1457m; 1383w; 1329w; 1297w; 1238s; 1176m; 1146m; 1072w; 1043w; 1015m; 895w; 856w; 814w; 765w; 721m; 692w; 648w; 612w; 578w; 521w; 439w.

Conclusions

We continue our research concerning the synthesis of some new 2-(4-methyl-phenoxymethyl)benzoic acid thioureides, in order to improve their antimicrobial and antifungal properties. The synthesized compounds have been characterized by melting point and solubility in various organic solvents and the chemical structure was confirmed by elemental analysis, NMR and IR spectroscopy. To obtain the compounds in high yield and high purity the optimal reaction conditions have been established. These thioureides are going to be tested in order to establish their antiinfectious activity.

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