Synthesis of New Thiourea Scaffold Compounds

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Thiourea derivatives are known to be biologically active compounds with a broad range of activities. As part of our interest in the synthesis and screening of potentially bioactive compounds, we report herein our results concerning the synthesis and spectroscopic properties of new benzoyl thiourea derivatives, 2-((4-methylphenoxy)methyl)-N-(phenylcarbamothioyl)benzamides.

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

It is well known that thiourea derivatives exhibit potent antibacterial [1], fungicidal [2], antitubercular [3], antitumor [4], antiviral [5, 6], analgesic [7] bioactivities and are also useful as insecticides [8, 9], fungicides [10], herbicides [11], and plant-growth regulators [12].

The compounds containing thiourea as structural fragment in their molecules are suitable candidates for chemical modeling as precursors in the synthesis of heterocyclic active derivatives.

The thioureides compounds are useful ligands in coordination chemistry, being studied their complexation behaviour, general characterization and biological activity, especially as cancerostatic agents [13].

Several works present new thiourea derivatives exhibiting good action against parasites [14, 15]. The search for compounds with anti-parasitic activity is a theme of continuous interest because of the urgent need to treat and control parasitic diseases.

In this paper we have been focusing on the preparation and characterization by physical and spectroscopic data of new benzoylthioureas derivatives. These compounds are in course of testing in order to establish their anti-parasitic activity.

Experimental part

All reagents used in this study were obtained from commercial suppliers (Merck, Fluka or Sigma-Aldrich) and used without further purification except *para*-methylphenol which was used freshly distilled, acetone was dried over K_2CO_3 and ammonium thiocyanate by heating at 100°C before use. The necessary liquid amines were dried with potassium hydroxide and afterwards distilled.

Melting points were determined in open capillary tubes on Electrothermal 9100 apparatus and are uncorrected.

Elemental analyses were done on a Perkin Elmer CHNS/O Analyzer Series II 2400 apparatus.

The IR spectra were recorded with a Bruker Vertex 70 spectrophotometer using the ATR technique. The IR bands are given as w – weak, m – medium, s – intense, vs – very intense.

^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO-d_6 on a Gemini 300BB instrument, at room temperature, operating at 300MHz for ^{1}H and 75MHz for ^{13}C and a Unity Inova 400 instrument, operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shifts were given as δ values in parts per million (ppm) relative to tetramethylsilane as internal standard and coupling constants J in Hz. Spin multiplets are given as s (singlet), d (doublet), dd (double doublet), dt (double triplet), dq (double quartet), t (triplet), td (triple doublet), tt (triple triplet), q (quartet), m (multiplet) and b (broad). The ^{13}C-NMR data are reported in the following order: chemical shifts and signal/ atom attribution (Cq-quaternary carbon).

The 2-(4-methyl-phenoxymethyl)benzoic acid and 2-(4-methyl-phenoxymethyl)benzoyl chloride derivatives were synthesized in good yields according to the method presented in a previous paper [16].

General synthesis procedure of the new thioureides

A solution of 2-(4-methylphenoxymethyl)benzoyl chloride (0.01 mol) in acetone (15 mL) was added to a solution of ammonium thiocyanate (0.01 mol) in acetone (5 mL). The reaction mixture was heated under reflux for 1 h, and then cooled to room temperature. A solution of primary amine (0.01 mol) in acetone (2 mL) was added to the mixture and heated under reflux for 1 h. The thioureide was precipitated after the cooled reaction mixture was poured into 500 mL water.

The solid product was purified by recrystallization from isopropanol with active carbon.

Results and discussions

The new derivatives (**1a-g**) were synthesized in good yields following the method described in [17].

The 2-(4-methyl-phenoxymethyl)benzoic acid (**2**) was converted into the corresponding benzoyl chloride (**3**) by treatment with thionyl chloride, using anhydrous 1,2-dichloroethane as reaction medium.

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

The 2-(4-methyl-phenoxymethyl)benzoyl chloride was treated with an equimolar quantity of ammonium thiocyanate in acetone to afford the corresponding isothiocianate intermediate which was not separated. Addition of an equimolar quantity of substituted amines in

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acetone to 2-(4-methyl-phenoxymethyl)benzoyl isothiocyanate (**6**) provided the new compounds.

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

The general synthetic pathway and structure of the investigated compounds are given in scheme 1.

The new compounds were characterized by melting point, elemental analysis, infrared and NMR spectral studies.

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

Elemental analysis, IR and NMR spectra confirmed the identity of the products.

Spectral data

The ^{1}H-NMR spectral data show two characteristic singlets of NH protons (for **1a**, **1b**,**1c**, **1d**, **1f**, **1g**) at δ 11.89- 12.12 ppm and 12.39- 12.60 ppm and the NH proton for **1e** is at 11.28 ppm as a singlet. The methylene group attached to the oxygen atom shows a singlet at δ 4.93- 5.33 ppm. The methyl group exhibited a characteristic singlet at δ 2.20- 2.24 ppm.

In the ^{13}CNMR spectra, the thiocarbonyl carbon showed a characteristic signal at δ 179.24- 183.74 ppm, the carbonyl carbon at δ 163.90- 171.06 ppm, the methylene carbon of CH_2Ogroup at δ 66.46- 68.16 ppm, and the methyl group at δ 19.94- 20.71 ppm.

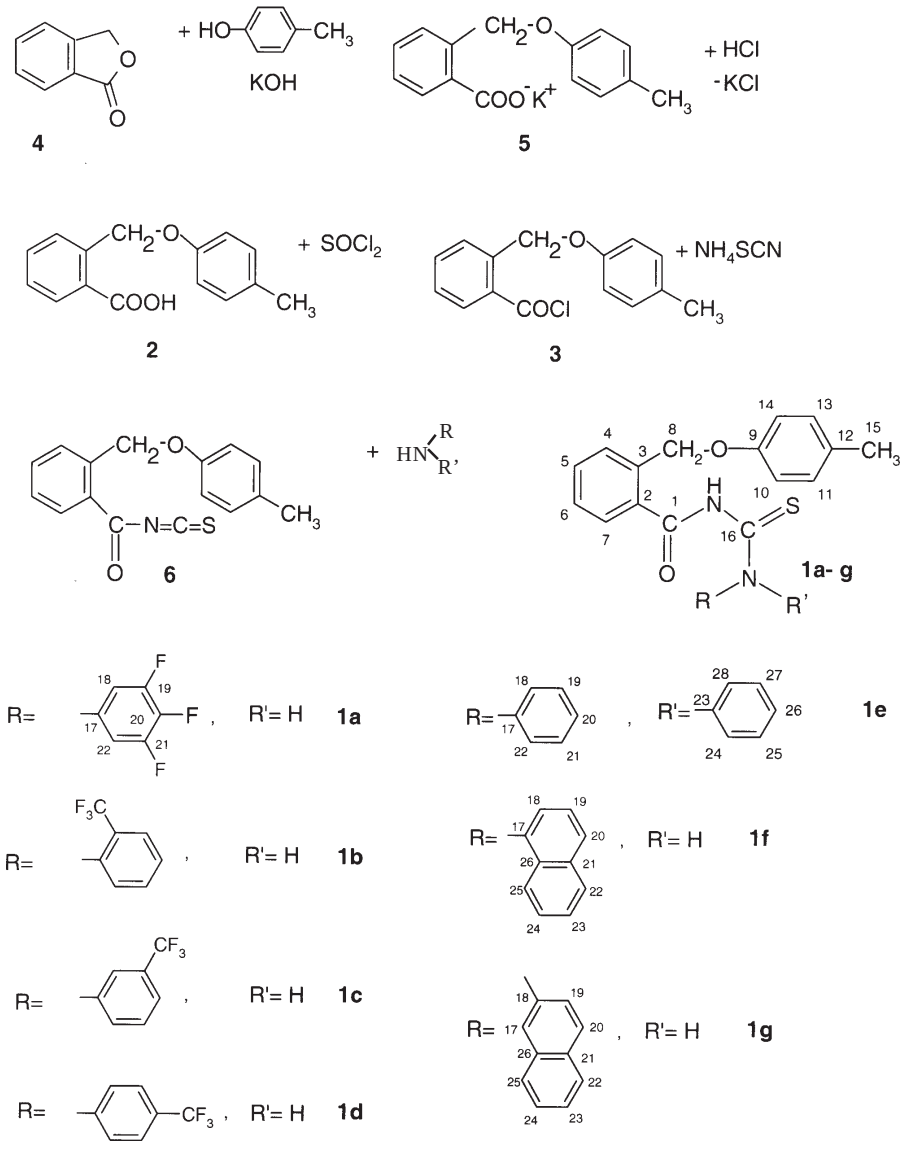
In the IR spectra the most characteristic absorptions are 3136- 3175 cm^{-1} and 3001- 3051 cm^{-1} (NH), 1671- 1697 cm^{-1} (C=O) and 1114- 1179 cm^{-1} (C=S).

2-((4-Methylphenoxy)methyl)-N-(3,4,5-trifluorophenylcarbamothioyl)benzamide (**1a**)

^{1}H-NMR (DMSO-d6, δ ppm, *J* Hz): 12.39(bs, 1H, NH); 12.00(bs, 1H, NH); 7.67÷7.54(m, 5H, H-4, H-5, H-7, H-18, H-22); 7.47(ddd, 1H, H-6, 2.4, 6.6, 8.9); 7.06(d, 2H, H-11, H-13, 8.6); 6.87(d, 2H, H-10, H-14, 8.6); 5.26(s, 2H, H-8); 2.21(bs, 3H, H-15).

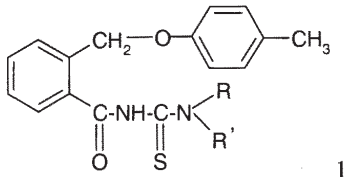
^{13}C-NMR (DMSO-d6, δ ppm): 179.60(C-16); 169.96(C-1); 156.06(C-9); 149.62(d, C-19, C-21, *J*(F-C)=259.2 Hz); 135.87(Cq); 134.06(C-20); 133.07(Cq); 133.02(Cq); 131.09(C-5); 129.74(C-11, C-13); 129.63(Cq); 128.44(C-4); 128.34(C-7); 127.70(C-6); 114.49(C-10, C-14); 109.60(C-18, C-22); 67.37(C-8); 19.94(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3168m; 3029m; 2919w; 2862w; 1689m; 1626w; 1611w; 1584w; 1555m; 1509vs; 1443s; 1369m; 1297m; 1252m; 1235m; 1211s; 1179s; 1143s; 1112m; 1079w; 1046s; 1016m; 826m; 815w; 758m; 739m; 716m; 655w; 590w.



Scheme 1. The new compounds synthesis

Table 1
DATA ON THE NEW THIOUREIDES **1a-g**



1a- g

Nr. crt.	R	R'	C%		H%		N%		S%		Melting point (^{0}C)	Yield (%)
			c.	e.	c.	e.	c.	e.	c.	e.		
1a.	-$C_6H_2F_3$ (3,4,5)	-H	61.39	61.07	3.98	4.06	6.51	6.56	7.45	7.44	131.2- 132.3	74
1b.	-$C_6H_4CF_3$(2)	-H	62.15	62.46	4.31	4.27	6.30	6.23	7.21	7.28	152.9- 153	69
1c.	-$C_6H_4CF_3$(3)	-H	62.15	62.51	4.31	4.33	6.30	6.39	7.21	7.17	141.3- 142.5	71
1d.	-$C_6H_4CF_3$(4)	-H	62.15	61.84	4.31	4.28	6.30	6.34	7.21	7.25	152- 153.2	79
1e.	-C_6H_5	-C_6H_5	74.31	74.65	5.35	5.29	6.19	6.21	7.08	7.11	148.9- 150.2	58
1f.	1-naphtyl	-H	73.21	73.57	5.20	5.26	6.57	6.63	7.52	7.54	194.4- 196.3	81
1g.	2-naphtyl	-H	73.21	73.49	5.20	5.22	6.57	6.52	7.52	7.54	169.6- 171.2	75

where: c = calculated, e = experimental

2-((4-Methylphenoxy)methyl)-N-(2-trifluoromethylphenylcarbamothioyl)benzamide (**1b**)

^{1}H-NMR(DMSO-d6, δ ppm, *J* Hz): 12.44(s, 1H, NH-C^{16}); 12.12(bs, 1H, NH); 7.79(dq, 1H, H-19, 1.0, 7.8, ^4J(F-H^{19})=0.7 Hz); 7.76÷7.69(m, 2H, H-20, H-22); 7.62(bd, 1H, H-7, 7.4); 7.58(dd, 1H, H-4, 2.1, 7.4); 7.55(td, 1H, H-5, 1.4, 7.4); 7.53(m, 1H, H-21); 7.47(td, 1H, H-6, 2.1, 7.5); 7.07(d, 2H, H-11, H-13, 8.6); 6.87(d, 2H, H-10, H-14, 8.6); 5.26(s, 2H, H-8); 2.21(bs, 3H, H-15).

^{13}C-NMR(DMSO-d6, δ ppm): 181.39(C-16); 170.61(C-1); 156.00(C-9); 135.77(Cq); 130.08(Cq); 132.67(CH); 131.11(C-5); 130.59(CH); 128.74(C-11, C-13); 128.65(Cq); 128.55(CH); 128.52(C-7); 127.77(C-6); 127.65(CH); 126.12(q, C-19, ^3J(F-C^{19})=5.1 Hz); 124.47(q, C-18, ^2J(F-C^{18})=42.5 Hz); 123.12(q, CF_3, *J*(F-C)=254.3 Hz); 114.53(C-10, C-14); 67.44(C-8); 20.01(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3163m; 3009m; 2901w; 1686m; 1609w; 1585w; 1507vs; 1457s; 1375w; 1318s; 1288m; 1256m; 1220m; 1154vs; 1106s; 1079m; 1057m; 1034m; 1010s; 956w; 873w; 818w; 761m; 738s; 665m; 651m; 595w; 536w.

2-((4-Methylphenoxy)methyl)-N-(3-trifluoromethylphenylcarbamothioyl)benzamide (**1c**)

^{1}H-NMR(DMSO-d6, δ ppm, *J* Hz): 12.48(s, 1H, NH); 11.95(bs, 1H, NH); 8.05(bs, 1H, H-18); 7.81(dt, 1H, H-22, 7.5, 2.1); 7.64(t, 1H, H-21, 7.5); 7.64÷7.55(m, 3H, H-4, H-7, H-20); 7.55(td, 1H, H-5, 1.4, 7.4); 7.47(td, 1H, H-6, 1.4, 7.5); 7.05(d, 2H, H-11, H-13, 8.6); 6.88(d, 2H, H-10, H-14, 8.6); 5.27(s, 2H, H-8); 2.20(bs, 3H, H-15).

^{13}C-NMR(DMSO-d6, δ ppm): 179.61(C-16); 170.04(C-1); 156.09(C-9); 138.67(Cq); 135.80(Cq); 133.25(Cq); 130.98(C-5); 129.75(CH); 129.71(C-11, C-13); 129.62(Cq); 129.11(q, C-19, *J*(F-C^{19})= 33 Hz); 128.68(C-4); 128.40(C-7); 128.30(CH); 127.72(C-6); 126.57(q, CF_3, *J*(F-C^{19})= 273 Hz); 122.75(q, C-20, *J*(F-C^{20})= 3.3 Hz); 121.10(q, C-18, *J*(F-C^{18})= 3.8 Hz); 114.47(C-10, C-14); 67.48(C-8); 19.94(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3338w; 3175w; 3028m; 1681m; 1600w; 1513vs; 1446s; 1382w; 1324s; 1230s; 1159vs; 1007s; 1077s; 1019m; 887w; 815w; 740m; 684m; 606w; 516w.

2-((4-Methylphenoxy)methyl)-N-(4-trifluoromethylphenylcarbamothioyl)benzamide (**1d**)

^{1}H-NMR(DMSO-d6, δ ppm, *J* Hz): 12.60(s, 1H, NH); 11.96(bs, 1H, NH); 7.88(d, 2H, H-18, H-22, 8.4); 7.77(d, 2H, H-19, H-21, 8.4); 7.62(bd, 1H, H-7, 7.4); 7.58(dd, 1H, H-4, 1.6, 7.4); 7.55(td, 1H, H-5, 1.4, 7.4); 7.46(td, 1H, H-6, 1.4, 7.5); 7.05(d, 2H, H-11, H-13, 8.6); 6.87(d, 2H, H-10, H-14, 8.6); 5.28(s, 2H, H-8); 2.20(s, 3H, H-15).

^{13}C-NMR(DMSO-d6, δ ppm): 179.24(C-16); 170.07(C-1); 156.05(C-9); 141.48(Cq); 135.86(Cq); 133.12(Cq); 131.04(C-5); 129.74(C-11, C-13); 129.63(Cq); 128.49(C-4); 128.29(C-7); 127.66(C-6); 126.11(q, C-20, ^3J(F-C^{20})=32.2 Hz); 125.67(q, C-19, C-21, ^3J(F-C$^{19-21}$)=3.7 Hz); 124.45(C-18, C-22); 124.04(q, CF_3, *J*(F-C)=270.0 Hz); 114.48(C-10, C-14); 67.40(C-8); 19.97(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3327w; 3001m; 1678m; 1599m; 1505vs; 1313s; 1226s; 1114vs; 1060m; 1020m; 835m; 813m; 795w; 738m; 671m; 600w; 509w.

2-((4-Methylphenoxy)methyl)-N-(diphenylcarbamothioyl)benzamide (**1e**)

^{1}H-NMR(DMSO-d6, δ ppm, *J* Hz): 11.28(s, 1H, NH-CO); 7.48(dd, 1H, H-7, 1.4, 7.8); 7.44(td, 1H, H-6, 7.8, 1.4); 7.37(dd, 4H, H-19, H-21 and H-25, H-27, 7.4, 8.6); 7.32(td, 1H, H-5, 7.4, 1.4); 7.29(dd, 4H, H-18, H-22 and H-24, H-28, 1.4, 8.6); 7.22(tt, 2H, H-20, H-26, 1.4, 7.4); 7.22(m, 1H, H-4); 7.08(d, 2H, H-11, H-13, 8.4); 6.81(d, 2H, H-10, H-14, 8.4); 4.93(s, 2H, H-8); 2.24(s, 3H, H-15).

^{13}C-NMR(DMSO-d6, δ ppm): 183.74(C-16); 163.90(C-1); 156.00(C-9); 145.59(C-17, C-26); 136.35(Cq); 132.73(Cq); 130.78(C-5); 129.73(C-11, C-13); 129.50(Cq); 129.08(C-19, C-21, C-25, C-27); 128.00(C-7); 127.70(C-4); 127.20(C-6); 127.11(C-20, C-26); 126.88(C-18, C-22, C-24, C-28); 114.74(C-10, C-14); 66.46(C-8); 20.04(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3152m; 3044w; 2958w; 2860w; 1697s; 1593w; 1498vs; 1451m; 1365vs; 1296m; 1244vs; 1219vs; 1168m; 1124m; 1063w; 1029m; 913w; 856w; 812m; 759m; 739m; 724m; 685s; 635w; 574w; 540w.

2-((4-Methylphenoxy)methyl)-N-(1-naphtylcarbamothioyl)benzamide (**1f**)

^{1}H-NMR(DMSO-d6, δ ppm, *J* Hz): 12.57(s, 1H, NH); 12.02(bs, 1H, NH); 7.99(bd, 1H, H-N, 8.2); 7.91(bd, 1H, H-N, 8.2); 7.77(bd, 1H, H-N, 8.0); 7.76(t, 1H, H-N, 7.8); 7.63-7.54(m, 4H, H-4, H-5, H-7, H-naphtyl); 7.50(td, 1H, H-N, 7.2, 2.0); 7.46(td, 1H, H-6, 1.4, 7.5); 7.09(d, 2H, H-11, H-13, 8.4); 6.94(d, 2H, H-10, H-14, 8.4); 5.33(s, 2H, H-8); 2.22(s, 3H, H-15).

^{13}C-NMR(DMSO-d6, δ ppm): 181.47(C-16); 171.06(C-1); 156.69(C-9); 136.29(Cq); 134.56(Cq); 134.21(Cq); 134.08(Cq); 131.47(C-5); 130.40(C-11, C-13); 130.19(Cq); 129.11(CH); 129.07(Cq); 129.05(CH); 128.83(CH); 128.33(C-4); 127.82(C-7); 127.11(C-6); 126.79(CH);

125.92(CH); 125.00(CH); 122.56(CH); 115.04(C-10, C-14); 68.16(C-8); 20.72(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3148m; 3051m; 1673m; 1597w; 1506vs; 1460m; 1381m; 1329w; 1298w; 1263m; 1240s; 1173s; 1157s; 1072w; 1046w; 1021m; 877w; 856w; 812m; 767m; 741m; 730m; 689w; 669w; 646w; 608w; 576w.

2-((4-Methylphenoxy)methyl)-N-(2-naphtylcarbamothioyl)benzamide (**1g**)

^{1}H-NMR(DMSO-d6, δ ppm, *J* Hz): 12.60(s, 1H, NH); 11.89(bs, 1H, NH); 8.21(bs, 1H, H-17); 7.95÷7.88(m, 3H, H-2-naphtyl); 7.69- 7.53(m, 5H, H-4, H-5, H-7, 2H-naphtyl); 7.47(td, 1H, H-6, 1.4, 7.5); 7.07(d, 2H, H-11, H-13, 8.5); 6.90(d, 2H, H-10, H-14, 8.5); 5.29(s, 2H, H-8); 2.20(s, 3H, H-15).

^{13}C-NMR(DMSO-d6, δ ppm): 179.48(C-16); 170.72(C-1); 156.65(C-9); 136.36(Cq); 13597(Cq); 133.82(Cq); 134.34(Cq); 131.79(Cq); 131.55(C-5); 130.34(C-11, C-13); 130.19(Cq); 129.04(CH); 128.89(CH); 128.60(CH); 128.27(C-4); 128.18(CH); 128.05(C-7); 127.08(C-6); 126.54(CH); 124.28(CH); 121.96(C-17); 115.09(C-10, C-14); 68.02(C-8); 20.59(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3318m; 3136w; 3023m; 2926w; 1671m; 1556s; 1502vs; 1383m; 1329s; 1221s; 1120s; 1019m; 886w; 855w; 813m; 738m; 675m; 602w; 512w; 468w.

Conclusions

The new benzoylthiourea derivatives are synthesized in three steps. The first step is the reaction of phtalide with potassium *para*-cresolate. In the second step the 2-(4-methyl-phenoxymethyl)benzoic acid react with thionyl chloride. The latter step is the reaction of 2-(4-methyl-phenoxymethyl)benzoic acid chloride with ammonium thiocianate to give the corresponding acylisothiocyanate and then with substituted amines to give the thiourea derivatives. Their structures were identified by spectral and elemental analysis.

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