Preparation of New Thiourea Derivatives with Potential Anti-parasitic and Antimicrobial Activity

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In this study new 2-(4-methyl-phenoxymethyl)benzoyl thioureas, N-[(R-amino)thioxomethyl]-2-[(4-methylphenoxy)methyl]benzamides, were synthesized by the reaction of 2-(4-methyl-phenoxymethyl)benzoyl isothiocyanate with different amines. Structures of the new compounds were identified by spectroscopic technique and also confirmed by elemental analysis. The compounds will be screened for their in vitro anti-parasitic, antibacterial and antifungal activity.

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

The appearance of multi-drug resistant microbial pathogens and intracellular or extracellular parasites determined the incessant need for the development of new classes of antimicrobial and anti-parasitic agents.

Keeping this fact in view, and as a continuation of our previous works on thiourea derivatives, it was thought of interest to synthesize, characterize and investigate the anti-parasitic and antimicrobial effects of new thioureides.

Our decision to evaluate these thioureides for anti-parasitic and antimicrobial activity was influenced by several reports disclosing these effects of thiourea- based and thioureides compounds[1-5], as well as the fact that thioureides with similar structure to that of the thioureides reported in this paper, show certain anti-parasitic characteristics on *Echinococcus multilocularis* and *Toxoplasma gondii* [6], and good antifungal activity against the *Candida albicans* and *Aspergillus niger* [7- 9].

Experimental part

All reagents and solvents were purchased from common comercial suppliers and were used without further purification, except *para*-methylphenol which was used freshly distilled. Previously the acetone was dried over potassium carbonate, the liquid amins over potassium hydroxide and freshly distilled and the ammonium thiocyanate by heating at 100^{0}C.

Melting points were estimated with a Electrothermal 9100 apparatus in open capillary tubes and are uncorrected.

The reaction was monitored by thin layer chromatography performed on silica gel plates 60F_{254} (Merck, 0.2 mm thick) using a mobile phase of 4:6 chloroform/ethyl acetate, with visualization by ultraviolet light.

Structural elucidation of these compounds was performed by IR, NMR spectroscopy and elemental analysis.

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

The NMR spectra were recorded on a Gemini 300BB instrument, at room temperature, operating at 300 MHz for ^{1}H and 75 MHz 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 recorded as δ values in parts per million (ppm) relative to TMS as an internal standard. Coupling constants (*J*) are reported in Hertz. Splitting patterns were designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet), td (triple doublet), br (broad).

The ^{13}C-NMR data are reported in as chemical shifts and signal/atom attribution (Cq- quaternary carbon).

The IR spectra were performed with a FT-IR Bruker Vertex 70 apparatus using the ATR technique. The IR bands are given as w – weak; m – medium; s – intense; vs – very intense.

The synthesis of 2-(4-methyl-phenoxymethyl)benzoic acid and 2-(4-methyl-phenoxymethyl)benzoyl chloride were realized according to the previous article data [10].

General procedure for the synthesis of the new thioureides

To a solution of ammonium thiocyanate (0.01 mol) in 5 mL dry acetone was added a solution of 2-(4-methyl-phenoxymethyl)benzoyl chloride (0.01 mol) in 15 mL dry acetone. The reaction mixture was refluxed one hour in a one round-bottom flask equipped with a condenser and a drying tube.

After cooling, 0.01 mol of primary aromatic amine in 2 mL dry acetone were added to the reaction mixture while stirring. The mixture was refluxed for one hour. The product was precipitated after the cooled reaction mixture was poured into 500 mL water. The raw obtained thioureides were few times crystallised from isopropanol with active charcoal.

Results and discussions

The new thioureides synthesis (**1a-n**) involve the reaction of 2-(4-methyl-phenoxymethyl)benzoyl chloride (**2**) with ammonium thiocyanate in dry acetone, followed by condensation of the resulting 2-(4-methyl-phenoxymethyl)-benzoyl isothiocyanate (**3**) with a primary amine.

The acide chloride (**2**) 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. First, the potassium salt of 2-(4-ethyl-phenoxymethyl)benzoic acid (**6**) is obtained and, having a good solubility in a 10% potassium hydroxide

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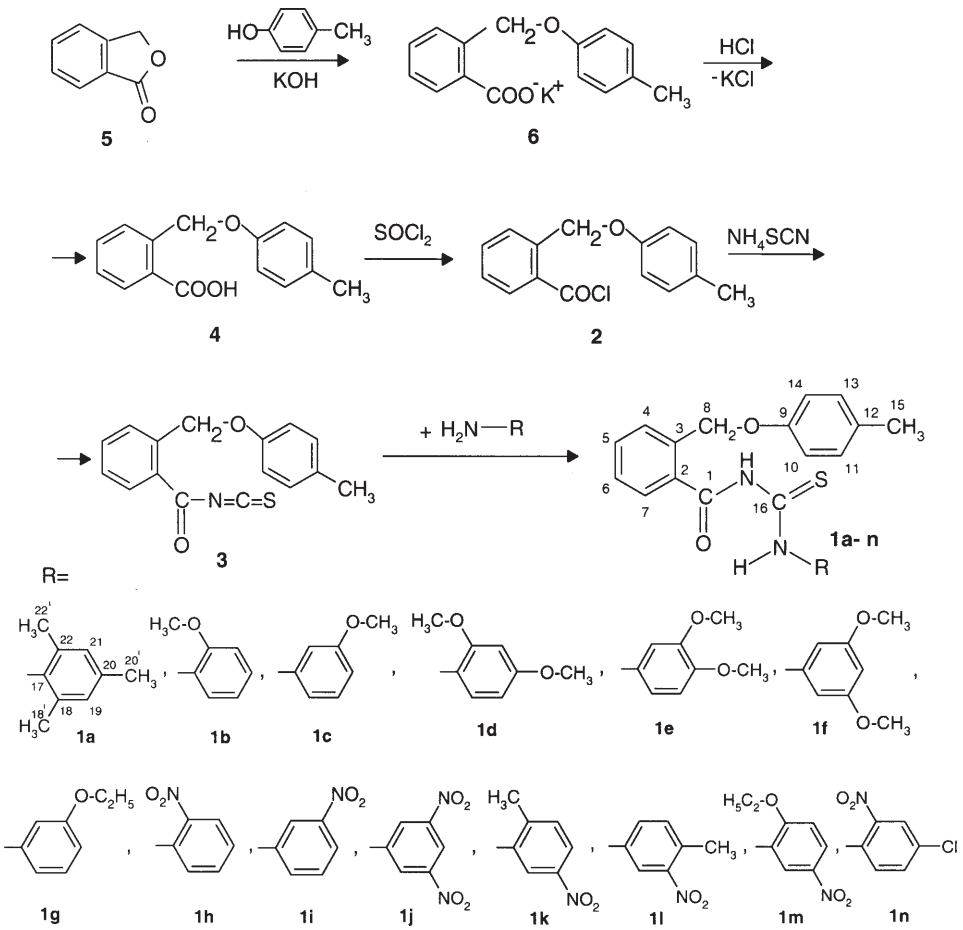

Scheme 1. The general scheme of synthesis

aqueous solution, can be separated 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.

The general synthetic pathway and the structure of the new compounds are given 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 elemental analysis, molecular weight, melting point and yield of the new thioureides are presented in table 1.

The structures of the obtained compounds were elucidated by spectral data.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(2,4,6-trimethylphenyl)-thiourea (**1a**)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 11.80(brs, 1H, NH); 11.63(brs, 1H, NH); 7.62(brd, 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); 7.06(d, 2H, H-11-13, 8.6); 6.90(s, 2H, H-19, H-21); 6.87(d, 2H, H-10-14, 8.6); 5.25(s, 2H, H-8); 2.24(s, 3H, H-20'); 2.22(s, 3H, H-15); 2.08(s, 6H, H-18', H-22').

Compound	C%		H%		N%		S%		Molecular weight	Melting point (^{0}C)	Yield (%)
	c.	e.	c.	e.	c.	e.	c.	e.			
1a.	71.74	71.91	6.26	6.33	6.69	6.57	7.66	7.74	418.55	183.1- 184.3	74
1b.	67.96	67.72	5.46	5.55	6.89	6.89	7.89	7.76	406.49	117.5- 118.3	81
1c.	67.96	67.66	5.46	5.41	6.89	6.78	7.89	7.86	406.49	137.1- 139	84
1d.	66.04	66.33	5.54	5.62	6.42	6.49	7.34	7.31	436.52	126.3- 127.5	76
1e.	66.04	66.39	5.54	5.50	6.42	6.37	7.34	7.27	436.52	140.6- 142.1	82
1f.	66.04	65.89	5.54	5.61	6.42	6.39	7.34	7.33	436.52	124.3- 125.7	79
1g.	68.55	68.30	5.75	5.83	6.66	6.67	7.62	7.51	420.52	107.4- 108.5	86
1h.	62.70	62.54	4.54	4.64	9.97	9.89	7.61	7.67	421.47	156.1- 157.3	83
1i.	62.70	62.51	4.54	4.57	9.97	9.92	7.61	7.66	421.47	148- 149.9	79
1j.	56.65	56.93	3.89	3.85	12.01	12.13	6.87	6.89	466.46	177.2- 178.7	77
1k.	63.43	63.75	4.86	4.74	9.65	9.66	7.36	7.27	435.49	143- 144.2	86
1l.	63.43	63.79	4.86	4.92	9.65	9.65	7.36	7.34	435.49	138.4- 139.1	88
1m.	61.92	61.57	4.98	4.85	9.03	9.12	6.89	6.84	465.52	165- 166.3	73
1n.	57.96	58.29	3.98	3.93	9.22	9.19	7.03	6.98	455.91	152.4- 154	87

where: c = calculated, e = experimental

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

^{13}C-NMR(dmso-d6, δ ppm): 180.19(C-16); 169.88(C-1); 156.03(C-9); 136.41(Cq); 135.56(Cq); 134.66(Cq); 133.56(Cq); 133.42(Cq); 130.83(C-5); 129.57(Cq); 128.68(C-4); 128.46(C-7); 128.37(C-19, C-21); 127.76(C-6); 129.69(C-11, C-13); 114.51(C-10, C-14); 67.50(C-8); 20.45(C-20'); 20.00(C-15); 17.60(C-18', C-22').

FT-IR(ATR in solid, νcm^{-1}): 3170m; 3004w; 2970w; 2917w; 2857w; 1684m; 1608m; 1583w; 1507vs; 1459s; 1388m; 1330w; 1292w; 1231s; 1169s; 1144s; 1073w; 1052w; 1032m; 878w; 849w; 807w; 745m; 726m; 685w; 522w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(2-methoxyphenyl)-thiourea (**1b**)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 12.76(brs, 1H, NH); 11.77(brs, 1H, NH); 8.53(m, 1H, H-22); 7.61(brd, 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); 7.22(m, 1H, H-20); 7.12(dd, 1H, H-19, 1.4, 8.4); 7.02(d, 2H, H-11-13, 8.6); 6.99(td, 1H, H-21, 8.0, 1.4); 6.87(d, 2H, H-10-14, 8.6); 5.26(s, 2H, H-8); 3.82(s, 3H, H-18'); 2.18(s, 3H, H-15).

^{13}C-NMR(dmso-d6, δ ppm): 177.52(C-16); 169.92(C-1); 155.98(C-9); 150.45(C-18); 135.59(Cq); 133.33(Cq); 129.58(Cq); 126.72(Cq); 130.88(C-5); 129.64(C-11, C-13); 128.47(C-4); 128.43(C-7); 127.69(C-6); 126.47(CH); 123.02(CH); 119.64(CH); 114.57(C-10, C-14); 111.23(C-19); 67.56(C-8); 55.90(C-18'); 19.96(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3403w; 3001w; 2834w; 1672w; 1600m; 1549vs; 1524vs; 1511vs; 1480m; 1462m; 1353s; 1320m; 1288m; 1235vs; 1178m; 1147s; 1129m; 1051m; 1028s; 947w; 818w; 803m; 752m; 725m; 681w; 574w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(3-methoxyphenyl)-thiourea (**1c**)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 12.44(s, 1H, NH, deuterable); 11.80(brs, 1H, NH, deuterable); 7.61(brd, 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, 7.8); 7.31(t, H-21, 7.8); 7.13(m, 1H, H-18); 7.06(d, 2H, H-11-13, 8.6); 6.87(d, 2H, H-10-14, 8.6); 6.84(m, 1H, H-20); 5.26(s, 2H, H-8); 3.77(s, 3H, H-19'); 2.20(s, 3H, H-15).

^{13}C-NMR(dmso-d6, δ ppm): 178.54(C-16); 170.08(C-1); 159.24(C-19); 156.04(C-9); 138.78(Cq); 135.74(Cq); 133.16(Cq); 129.61(Cq); 130.94(C-5); 129.71(C-11, C-13); 129.34(C-21); 128.42(C-4); 128.27(C-7); 127.64(C-6); 116.12(C-18); 114.61(C-10, C-14); 111.78(C-20); 109.55(C-22); 67.44(C-8); 55.15(C-19'); 19.97(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3355w; 3001w; 2829w; 1677m; 1595m; 1557s; 1506vs; 1461s; 1383w; 1333m; 1289s; 1229vs; 1141s; 1030s; 898w; 847m; 781m; 753m; 736m; 727m; 662m; 606w; 518w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(2,4-dimethoxyphenyl)-thiourea (**1d**)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 12.55(s, 1H, NH, deuterable); 11.69(brs, 1H, NH, deuterable); 8.30(d, H-22, 8.9); 7.61(brd, 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, 7.8); 7.04(d, 2H, H-11-13, 8.6); 6.86(d, 2H, H-10-14, 8.6); 6.67(d, 1H, H-19, 2.5); 6.56(dd, 1H, H-21, 2.5, 8.9); 5.25(s, 2H, H-8); 3.80(s, 3H, H-18' or H-20'); 3.79(s, 3H, H-18' or H-20'); 2.20(s, 3H, H-15).

^{13}C-NMR(dmso-d6, δ ppm): 177.50(C-16); 169.90(C-1); 158.07(C-18 or C-20); 155.99(C-9); 151.94(C-18 or C-20); 135.58(Cq); 133.34(Cq); 129.59(Cq); 119.89(C-17);

130.84(C-5); 129.66(C-11, C-13); 128.46(C-4); 128.41(C-7); 127.68(C-6); 114.59(C-10, C-14); 103.80(C-21; 98.59(C-19); 124.42(C-22);

67.55(C-8); 55.94(C-18' or C-20'); 55.33(C-18' or C-20'); 19.97(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3176w; 3030w; 2944w; 1670m; 1613m; 1536vs; 1508vs; 1465m; 1380w; 1324m; 1283m; 1258m; 1231vs; 1207s; 1160vs; 1128m; 1069w; 1028s; 949w; 825m; 798m; 742m; 722m; 671w; 628w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(3,4-dimethoxyphenyl)-thiourea (**1e**)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 12.32(s, 1H, NH, deuterable); 11.75(brs, 1H, NH, deuterable); 7.61(brd, 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, 7.8); 7.28(dd, 1H, H-22, 2.5, 8.6); 7.12(d, 1H, H-18, 2.5); 7.07(d, 2H, H-11-13, 8.6); 6.97(d, 1H, H-21, 8.6); 6.88(d, 2H, H-10-14, 8.6); 5.26(s, 2H, H-8); 3.77(s, 3H, H-19' or H-20'); 3.75(s, 3H, H-19' or H-20'); 2.21(s, 3H, H-15).

^{13}C-NMR(dmso-d6, δ ppm): 178.51(C-16); 169.96(C-1); 156.05(C-9); 148.29(C-19 or C-20); 147.02(C-19 or C-20); 135.69(Cq); 133.25(Cq); 130.68(Cq); 129.64(Cq);

130.90(C-5); 129.72(C-11, C-13); 128.39(C-4); 128.27(C-7); 127.64(C-6); 116.41(C-18); 114.55(C-10, C-14); 111.39(C-21); 108.77(C-22); 67.55(C-8); 55.94(C-18' or C-20'); 55.33(C-18' or C-20'); 19.97(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3182w; 3027w; 3002w; 2954w; 2830w; 1678s; 1612w; 1530vs; 1508vs; 1455s; 1434m; 1412m; 1379w; 1333w; 1287m; 1264s; 1235vs; 1201m; 1169s; 1134vs; 1069w; 1019s; 816m; 767w; 735s; 662m; 568w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(3,5-dimethoxyphenyl)-thiourea (**1f**)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 12.42(s, 1H, NH, deuterable); 11.79(brs, 1H, NH, deuterable); 7.61(brd, 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, 7.8); 7.05(d, 2H, H-11-13, 8.6); 6.88(d, 2H, H-18, H-22, 2.2); 6.87(d, 2H, H-10-14, 8.6); 6.42(t, 1H, H-20, 2.2); 5.26(s, 2H, H-8); 3.75(s, 6H, H-19' and H-21'); 2.20(s, 3H, H-15).

^{13}C-NMR(dmso-d6, δ ppm): 178.38(C-16); 170.00(C-1); 160.21(C-19 and C-21); 156.04(C-9); 139.24(Cq); 135.74(Cq); 133.17(Cq); 129.61(Cq); 130.95(C-5); 129.71(C-11, C-13); 128.42(C-4); 128.27(C-7); 127.64(C-6); 114.52(C-10, C-14); 102.01(C-18, C-22); 98.20(C-20); 67.43(C-8); 55.27(C-19' and C-21'); 19.96(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3282w; 3152w; 3001w; 2912w; 2835w; 1668m; 1607vs; 1529vs; 1513vs; 1461s; 1425m; 1348m; 1308m; 1238s; 1206s; 1147vs; 1124m; 1071m 1035m; 932w; 895w; 852m; 814m; 801m; 751m; 690m; 661s; 631m; 607w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(3-ethoxyphenyl)-thiourea (**1g**)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 11.80(brs, 1H, NH); 11.73(brs, 1H, NH); 7.62(brd, 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); 7.45(dd, 1H, H-22, 2.4, 8.2); 7.34(t, 1H, H-18, 2.4); 7.29(t, 1H, H-21, 8.2); 7.06(d, 2H, H-11, H-13, 8.6); 6.87(d, 2H, H-10, H-14, 8.6); 6.82(dd, 1H, H-20, 2.4, 8.2); 5.26(s, 2H, H-8); 4.04(q, 2H, H-19', 7.1); 2.21(s, 3H, H-15); 1.34(t, 3H, H-19", 7.1).

^{13}C-NMR(dmso-d6, δ ppm): 178.95(C-16); 170.05(C-1); 158.493(C-19); 156.08(C-9); 138.87(Cq); 135.77(Cq); 133.32(Cq); 130.96(C-5); 129.63(C-11, C-13); 129.38(Cq); 128.44(C-7); 128.30(C-4); 127.67(C-6); 125.80(C-21); 116.05(C-22); 114.57(C-10, C-14); 112.35(C-20); 110.06(C-18); 67.47(C-8); 63.15(C-19'); 20.00(C-15); 14.53(C-19").

FT-IR(ATR in solid, ν cm^{-1}): 3343w; 3031w; 2982w; 2931w; 1673m; 1591m; 1559s;1505vs; 1455m; 1388w; 1346m; 1314m; 1292m; 1261m; 1227vs; 1190m; 1164m; 1140vs; 1117m; 1051m; 1026m; 956w; 929w; 866w; 828w; 777m; 738m; 673m; 558w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(2-nitrophenyl)-thiourea (**1h**)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 12.74(s, 1H, NH, deuterable); 12.08(brs, 1H, NH, deuterable); 8.18(dd, 1H, H-19, 1.4, 8.2); 7.90(td, 1H, H-21, 8.2, 1.4); 7.78(td, 1H, H-20, 1.6, 8.2); 7.61(brd, 1H, H-7, 7.4); 7.58(dd, 1H, H-4, 1.6, 7.4); 7.57(dd, 1H, H-22, 1.6, 8.2); 7.55(td, 1H, H-5, 1.4, 7.4); 7.46(td, 1H, H-6, 1.4, 7.8); 7.06(d, 2H, H-11, H-13, 8.6); 6.88(d, 2H, H-10-14, 8.6); 5.28(s, 2H, H-8); 2.21(s, 3H, H-15).

^{13}C-NMR(dmso-d6, δ ppm): 180.31(C-16); 169.86(C-1); 155.96(C-9); 143.77(C-18); 135.81(Cq); 133.08(Cq); 131.86(Cq); 129.62(Cq); 133.56(C-20); 131.07(C-5); 129.72(C-11, C-13); 129.59(C-21); 128.51(C-4); 128.39(C-7); 127.71(C-22); 127.63(C-6); 124.76(C-19); 114.54(C-10, C-14); 67.42(C-8); 19.99(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3175m; 3032w; 2908w; 2865w; 1696m; 1606w; 1583m; 1504vs; 1467s; 1373w; 1339m; 1286m; 1228s; 1166s; 1143m; 1106m; 1074m; 1025m; 873w; 787w; 761m; 741m; 656m; 514w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(3-nitrophenyl)-thiourea (**1i**)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 12.54(s, 1H, NH, deuterable); 12.00(brs, 1H, NH, deuterable); 8.65(dt, 1H, H-20, 8.5, 2.1); 8.12(dt, 1H, H-22, 8.5, 2.1); 7.94(m, 1H, H-18); 7.69(t, 1H, H-21, 8.5); 7.61(brd, 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, 7.8); 7.06(d, 2H, H-11, H-13, 8.6); 6.88(d, 2H, H-10-14, 8.6); 5.28(s, 2H, H-8); 2.20(s, 3H, H-15).

^{13}C-NMR(dmso-d6, δ ppm): 179.50(C-16); 169.84(C-1); 156.06(C-9); 147.42(C-19); 139.92(Cq); 135.82(Cq); 133.12(Cq); 129.65(Cq); 131.04(C-18); 130.91(C-5); 129.85(C-21); 129.71(C-11, C-13); 128.40(C-4); 128.28(C-7); 127.68(C-6); 120.76(C-22); 118.91(C-20); 114.47(C-10, C-14); 67.44(C-8); 19.95(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3160m; 3033w; 2920w; 1680m; 1614w; 1585w; 1512vs; 1471s; 1384w; 1344s; 1313m; 1281m; 1245s; 1227s; 1173s; 1150m; 1089w; 1070w; 1028m; 808m; 772w; 741m; 696m; 678m; 660w; 506w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(3,5-dinitrophenyl)-thiourea (**1j**)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 12.64(brs, 1H, NH); 12.16(brs, 1H, NH); 8.93(d, 2H, H-18, H-22, 2.2); 8.69(t, 1H, H-20, 2.2); 7.62(brd, 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); 7.06(d, 2H, H-11-13, 8.6); 6.89(d, 2H, H-10-14, 8.6); 5.28(s, 2H, H-8); 2.19(s, 3H, H-15).

^{13}C-NMR(dmso-d6, δ ppm): 180.10(C-16); 169.71(C-1); 156.09(C-9); 147.53(C-19, C-21); 140.16(Cq); 135.92(Cq); 133.10(Cq); 131.16(C-5); 129.78(Cq); 128.75(C-11, C-13); 128.34(C-7); 127.75(C-6); 124.86(C-18, C-22); 115.50(C-20); 114.49(C-10, C-14); 67.47(C-8); 19.97(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3316w; 3086w; 3029w; 2913w; 1677w; 1600w; 1541s; 1506vs; 1384w; 1339s; 1308m; 1269w; 1222m; 1155w; 1070m; 1054w; 1025m; 921w; 891w; 854m; 830w; 810w; 751m; 726s; 695m; 660w; 616w; 562w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(2-methyl-5-nitrophenyl)-thiourea (**1k**)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 12.16(bs, 2H, NH, deuterable); 8.56(d, 1H, H-22, 2.5); 8.07(dd, 1H, H-20, 2.5, 8.4); 7.64(d, 1H, H-19, 8.4); 7.61(brd, 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); 7.06(d, 2H, H-11-13, 8.6); 6.88(d, 2H, H-10-14, 8.6); 5.27(s, 2H, H-8); 2.26(s, 3H, H-18'); 2.21(s, 3H, H-15).

^{13}C-NMR(dmso-d6, δ ppm): 179.92(C-16); 170.17(C-1); 156.09(C-9); 145.44(C-21); 141.69(Cq); 137.87(Cq); 135.66(Cq); 133.38(Cq); 131.36(C-19); 130.89(C-5); 129.70(C-11, C-13); 129.66(Cq); 128.40(C-4); 127.73(C-7); 127.72(C-6); 121.22(C-20); 120.99(C-22); 114.42(C-10, C-14); 67.57(C-8); 19.96(C-15); 17.63(C-18').

FT-IR(ATR in solid, ν cm^{-1}): 3170m; 3006m; 1686m; 1605m; 1557m; 1506vs; 1455s; 1373w; 1331vs; 1265m; 1231m; 1195s; 1151s; 1121s; 1084s; 1010m; 950w; 899w; 861w; 822m; 799m; 733s; 667w; 645w; 626w; 566w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(3-nitro-4-methylphenyl)-thiourea (**1l**)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 12.39(s, 1H, NH, deuterable); 11.99(brs, 1H, NH, deuterable); 8.37(d, 1H, H-18, 2.2); 7.75(dd, 1H, H-22, 8.2); 7.61(brd, 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); 7.54(d, 1H, H-21, 8.2); 7.47(td, 1H, H-6, 1.4, 7.8); 7.05(d, 2H, H-11-13, 8.6); 6.88(d, 2H, H-10-14, 8.6); 5.27(s, 2H, H-8); 2.50(s, 3H, H-20'); 2.20(s, 3H, H-15).

^{13}C-NMR(dmso-d6, δ ppm): 179.34(C-16); 169.89(C-1); 156.05(C-9); 148.16(C-19); 136.70(Cq); 135.80(Cq); 133.19(Cq); 132.73(C-21); 130.97(C-5); 130.48(Cq); 129.70(C-11, C-13); 129.62(C-22); 129.36(Cq); 128.40(C-4); 128.24(C-7); 127.65(C-6); 119.98(C-18); 114.48(C-10, C-14); 67.43(C-8); 19.95(C-15); 19.19(C-20').

FT-IR(ATR in solid, ν cm^{-1}): 3351m; 3197m; 3028w; 2932w; 2871w; 1692m; 1588m; 1548s; 1522vs; 1505vs; 1460m; 1379m; 1339s; 1286m; 1260m; 1233s; 1216m; 1157s; 1066m; 1041w; 1020m; 945w; 826m; 798m; 760m; 737m; 688m; 659m; 593m; 518w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(2-ethoxy-5-nitrophenyl)-thiourea (**1m**)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 13.24(s, 1H, NH, deuterable); 12.01(brs, 1H, NH, deuterable); 9.91(bs, 1H, H-22); 8.13(dd, 1H, H-20, 2.7, 9.0); 7.61(brd, 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, 7.8); 7.30(d, 1H, H-19, 9.0); 6.97(d, 2H, H-11-13, 8.6); 6.83(d, 2H, H-10-14, 8.6); 5.26(s, 2H, H-8); 4.23(q, 2H, H-18', 6.9); 2.14(s, 3H, H-15); 1.36(t, 3H, H-18", 6.9).

^{13}C-NMR(dmso-d6, δ ppm): 177.67(C-16); 170.26(C-1); 156.03(C-9); 154.23(C-18); 139.47(Cq); 135.79(Cq); 133.09(Cq); 130.99(C-5); 129.56(C-11, C-13); 129.53(Cq); 128.49(C-4); 128.41(C-7); 127.70(C-6); 127.50(Cq); 121.89(C-20); 115.96(C-22); 114.40(C-10, C-14); 111.59(C-19); 67.54(C-8); 65.54(C-18'); 19.90(C-15); 14.03(C-18").

FT-IR(ATR in solid, ν cm^{-1}): 3262m; 3095w; 2990m; 1678m; 1592m; 1557vs; 1511vs; 1492s; 1472s; 1445m; 1384w; 1360m; 1337s; 1320s; 1292m; 1268s; 1257m; 1242s; 1225s; 1174m; 1155s; 1133m; 1116m; 1081m; 1053w; 1029s; 929w; 900w; 809m; 789w; 775m; 742m; 686w; 642w; 566w.

N-[2-(4-Methyl-phenoxymethyl)-benzoyl]-N'-(4-chloro-2-nitrophenyl)-thiourea (**1n**)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 12.67(brs, 1H, NH); 12.14(brs, 1H, NH); 8.19(d, 1H, H-19, 2.4); 7.93(d, 1H, H-22, 8.6); 7.85(dd, 1H, H-21, 2.4, 8.6); 7.62(brd, 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); 7.06(d, 2H, H-11, H-13, 8.6); 6.88(d, 2H, H-10, H-14, 8.6); 5.27(s, 2H, H-8); 2.21(s, 3H, H-15).

^{13}C-NMR(dmso-d6, δ ppm): 180.50(C-16); 169.82(C-1); 155.95(C-9); 144.17(Cq); 135.84(Cq); 132.99(Cq); 132.32(Cq);131.15(Cq); 129.63(Cq); 133.28(C-21); 131.27(C-22); 131.11(C-5); 129.72(C-11, C-13); 128.52(C-7); 128.38(C-4); 127.69(C-6); 124.52(C-19); 114.54(C-10, C-14); 67.40(C-8); 20.00(C-15).

FT-IR(ATR in solid, ν cm^{-1}): 3147m; 3068m; 3001m; 2872w; 1694m; 1607w; 1569w; 1501vs; 1379w; 1343m; 1318m; 1282m; 1237s; 1167s; 1106m; 1072w; 1018w; 883w; 837w; 811w; 764m; 737m; 654w; 610w.

In the ^{1}H-NMR spectra the chemical shift of N-H protons was found as two characteristic broad singlets in the range of δ 11.8- 12.76 ppm and 11.63- 12.67 ppm. The aromatic protons produce signals in the range δ 6.83- 9.91 ppm. The methylene group situated near the oxygen produces a singlet at δ 5.25-5.28 ppm. Methyl protons on the phenoxymethyl moiety were calculated in the range of δ 2.14- 2.22 ppm.

Carbon atom of the thiocarbonyl group at δ 180.5- 177.5 ppm showed the highest values. ^{13}C-NMR signals of the carbonyl group appear at δ 169.71- 170.26 ppm. The methylene carbon near the oxygen produces a signal at δ 67.40–67.57 ppm, and the methyl carbon (C-15) at δ 19.9–20.0 ppm.

The compounds were characterized by the appearance of the characteristic peaks for C=O and C=S at 1696- 1668 cm^{-1} and 1178- 1148 cm^{-1}, respectively, in addition to the methylen peaks at 2932- 2908 in the IR spectra.

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

Conclusions

This study reports the synthesis and characterization of new thioureides of 2-(4-methyl-phenoxymethyl)benzoic acid. Substituted aroyl chloride was treated with ammonium thiocyanate in acetone to afford the corresponding isothiocyanate which was not separated followed by reaction with amines to furnish the acylthiourea derivatives. Substituted benzoic acid was converted into corresponding aroyl chloride by treatment with thionyl chloride. The structure of the new compounds was confirmed by the spectral data and the elemental analysis. These compounds are in process of testing in order to establish their anti-parasitic and antimicrobial activity.

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