SYNTHESIS AND STRUCTURAL EVALUATION OF NEW 2-((4-CHLOROPHENOXY)METHYL)-N-(ARYLCARBAMOTHIOYL)BENZAMIDES

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Abstract
The present work describes an efficient method to obtain new derivatives of 2-((4-chlorophenoxy)methyl)-N-(arylcarbamothioyl)benzamide of biological interest. The synthesized derivatives were characterized by IR, $^1$H-NMR, $^{13}$C-NMR and elemental analyses.

Rezumat
Această lucrare prezintă o metodă eficientă pentru obținerea unor noi derivații 2-((4-clorofenoxi)metil)-N-(arilcarbamotioyl)benzamidei cu potențial biologic. Compușii sintetizați au fost caracterizați prin intermediul datelor furnizate de analiza elementală și cea spectrală IR, $^1$H-RMN, și $^{13}$C-RMN.

Keywords: thiourea derivatives, benzamides, IR, $^1$H-NMR, $^{13}$C-NMR spectroscopy

Introduction

Taking into consideration the aforementioned biological significance of thioureas, synthesis of some new 2-((4-chlorophenoxy)methyl)-N-(arylcarbamothioyl)benzamides derivatives was undertaken as a continuation of our efforts towards synthesis and characterisation of new thiourea derivatives [3, 6].

Materials and Methods
Chemical substances and solvents were purchased from Merck- Darmstadt (Germany) and Aldrich-Steinheim (Germany) Companies and were used as received, excepting the solvents which were purified by distillation. Acetone and 1,2-dichloroethane were dried over calcium chloride. Ammonium thiocyanate was dried by heating at 100°C and then used in the reactions. Melting points were obtained using an Electrothermal 9100 capillary melting point apparatus (Bibby Scientific Ltd, Stone, UK) in open capillary tubes; the values reported here are uncorrected.

Elemental analysis was carried out using a PerkinElmer 2400 Series II CHNS/O Elemental Analyzer (Waltham, MA, USA). The obtained results were within ± 0.4% of the theoretical values. The Fourier-transform infrared (FT-IR) spectra of all synthesized compounds were run on a Bruker Vertex 70 FT-IR spectrometer (Bruker Corporation, Billerica, MA, USA).

$^1$H-NMR and $^{13}$C-NMR spectra were recorded in hexadeuteriodimethyl sulphoxide (DMSO-d6) on a Varian Gemini 300BB instrument (Varian Medical Systems, Palo Alto, CA, USA) operating at 300.0 MHz for proton ($^1$H)-NMR, and 75.0 MHz for carbon-13 ($^{13}$C)-NMR.

The obtaining of the targeted compounds (1a-i) was straightforward as outlined in Figure 1.

New compounds with the thiourea skeleton were obtained starting from phthalide (2) which was treated with potassium p-chlorophenoxide in xylene to give the potassium salt of 2-(4-chlorophenoxymethyl)benzoic acid (3). This was treated with a mineral acid solution to precipitate...
the 2-(4-chlorophenoxy)methylbenzoic acid (4). The mentioned acid was treated with thionyl chloride to obtain 2-(4-chlorophenoxy)methyl benzoyl chloride (5), using anhydrous 1,2-dichlorehthane as reaction medium. Then, the acid chloride was treated with potassium thiocyanate in acetone to obtain the corresponding isothiocyanate intermediates (6) which were not separated. Condensation of the isothiocyanates with alkyl isoalkylanilines furnished the 2-((4-chlorophenoxy)methyl)-N-(arylcarbamothioyl)benzamides.

\[
\begin{align*}
\text{2} & \xrightarrow{\text{KOH}} \text{3} \\
\text{4} & \xrightarrow{\text{30Cl}_2} \text{5} \\
\text{6} & \xrightarrow{\text{H_2N-R}} \text{1a-i}
\end{align*}
\]

Figure 1.

Synthetic pathway for obtaining the new 2-((4-chlorophenoxy)methyl)-N-(arylcarbamothioyl)benzamides (1a-i)

**Results and Discussion**

The new benzamides are white solids, soluble at room temperature in acetone and chloroform, by heating in lower alcohols, benzene, toluene and xylene and insoluble in water. The purity and identity of these compounds were confirmed with the help of infrared and NMR spectral studies and other physico-chemical measurements. The IR bands were given as w – weak, m – medium, s – strong, vs – very strong.

The thiourea derivatives are characterized by IR absorptions at 3263–3135 cm\(^{-1}\) for the νN-H of the thioamide group. These compounds show antisymmetric stretching vibrations for the νC-H of the methyl and methylene groups, in the 2969–2957 cm\(^{-1}\) and 2932–2923 cm\(^{-1}\) range, respectively. These spectra revealed the presence of the medium-strong νC=O absorption band in the region 1683–1660 cm\(^{-1}\). The IR spectra showed very strong characteristic vibrations of the 6N-H amide group at 1524–1490 cm\(^{-1}\). These compounds also showed typical alkyl-aryl ether at 1262–1226 cm\(^{-1}\).
isopropanol. The mixture was poured into water. The solid product was filtered and purified by recrystallization from isopropanol.

The compounds structures are also supported by NMR measurements. The new benzamides were dissolved in DMSO-d6 (hexadeuteriodimethyl sulfoxide) and the chemical shifts values, expressed in parts per million (ppm), were referenced downfield to tetramethylsilane and the constants (J) values in Hertz.

The 1H-NMR data are reported in the following order: chemical shifts, multiplicity, the coupling constants, number of protons and signal/ atom attribution. The apparent resonance multiplicity is described as s (singlet), d (doublet), t (triplet), q (quintet ), sext (sextet), sept (septet), m (multiplet), dd (double doublet), td (triple doublet), and br (broad) signal.

In the 1H NMR spectra, the methylene group attached to the oxygen atom showed a singlet at δ 5.22–5.32 ppm. The signals of aromatic protons appeared in a range of δ 6.89–7.63 ppm with the intensity and multiplicity according to each aromatic spin system. The NH protons exhibited two characteristic broad singlets or singlets at δ 11.75–11.95 ppm and δ 12.10–12.39 ppm, the most acidic being the NH near C=S group which is probably involved in six member ring structure by a hydrogen bond with neighbour C=O group, respectively.

For the 13C-NMR data the following order was applied: chemical shifts and signal/ atom attribution (Cq= quaternary carbon).

In the 13C NMR spectra, the thiocarbonyl carbon showed a characteristic signal at δ 178.61–180.77 ppm, the carbonyl carbon at δ 169.98–170.60 ppm, the methylene carbon of CH2O group at δ 67.70–67.87 ppm. Chemistry

The intermediates were prepared using the previously reported method [5].

General procedure for the synthesis of the new thioureides 1a-i

A solution of 2-(4-chlorophenoxy)methyl-benzoyl chloride (5, mol. wt. 281.39, 0.01 mol) in acetone (15 mL, dried over potassium carbonate) was added dropwise to a suspension of ammonium thiocyanate (mol. wt. 76.13, 0.76 g, 0.01 mol, dried by heating at 100°C) 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 mole) in acetone (5 mL) was added and the resulting mixture was stirred for 1 h. The reaction mixture was poured into water. The solid product was filtered and purified by recrystallization from isopropanol.

Spectral data

2-((4-Chlorophenoxy)methyl)-N-(2-n-propyl-phenylcarbamothioyl)benzamide (1a)

Yield 56%; mp 119-120.2°C.

1H-NMR (DMSO-d6, T= 298K): δ 12.21 (s, 1H, NH, deuterable), 11.91 (s, 1H, NH, deuterable), 7.63 (dd, 1H, J = 1.2 Hz, J = 7.4 Hz, H-7), 7.61-7.53 (m, 2H, H-4, H-5); 7.54-7.47 (m, 2H, H-6, H-22), 7.32 (d, 2H, J = 9.0 Hz, H-11, H-13), 7.30-7.16 (m, 3H, H-19, H-20, H-21), 7.01 (d, 2H, J = 9.0 Hz, H-10, H-14), 5.30 (s, 2H, H-8), 2.44 (t, 2H, J = 7.5 Hz, H-23), 1.46 (sxt, 2H, J = 7.6 Hz, H-24), 0.78 (t, 3H, J = 7.6 Hz, H-25) ppm.

13C-NMR (DMSO-d6, T=298K): δ 180.10 (C-16), 170.34 (C-1), 157.04 (C-9), 137.05 (Cq), 135.05 (Cq), 133.48 (Cq), 124.71 (Cq), 130.98 (CH), 129.60 (CH), 129.20 (C-11, C-13), 128.76 (CH), 128.53 (CH), 127.98 (CH), 126.96 (CH), 125.97 (CH), 116.35 (C-10, C-14), 67.87 (C-8), 32.91 (C-23), 22.92 (C-24), 13.52 (C-25) ppm.

FT-IR(solid in ATR): ν 3275 w, 3162 m, 3029 w, 2958 m, 2929 w, 2869 w, 1666 m, 1642 m, 1583 m, 1570 m, 1490 vs, 1446 s, 1377 w, 1334 w, 1285 m, 1219 s, 1195 m, 1178 m, 1163 m, 1102 w, 1035 m, 817 m, 746 m, 684 m, 659 m cm⁻¹.

Anal. calcd. for C26H24ClN2S (438.97): C, 65.67; H, 5.82; N, 6.38; S, 7.30%; Found: C, 65.41; H, 5.89; N, 6.30; S 7.19%.

2-((4-Chlorophenoxy)methyl)-N-(2-iso-propyl-phenylcarbamothioyl)benzamide (1c)

Yield 54%; mp 138.1-138.9°C.

1H-NMR (DMSO-d6, T= 298K): δ 12.34 (bs, 1H, NH, deuterable), 11.75 (bs, 1H, NH, deuterable), 7.62 (d, 1H, J = 7.7 Hz, H-7), 7.60-7.55 (m, 2H, H-4, H-5), 7.49 (m, 1H, H-6); 7.49(d, 2H, J = 8.5 Hz, H-18, H-22), 7.31 (d, 2H, J = 9.0 Hz, H-11, H-13), 7.22 (d, 2H, J = 8.5 Hz, H-19, H-21), 7.01 (d, 2H, J = 9.0 Hz, H-10, H-14), 5.31 (s, 2H, H-8) ppm.

13C-NMR (DMSO-d6, T=298K): δ 178.82 (C-16), 170.13 (C-1), 157.06 (C-9), 140.36 (C-20), 135.53 (Cq), 135.29 (Cq), 133.38 (Cq), 124.72 (Cq), 131.12 (CH), 129.30 (C-11, C-13), 128.64 (CH), 128.50 (CH), 128.49 (C-18, C-22), 127.95 (CH), 124.18 (C-19, C-21), 116.49 (C-10, C-14), 67.83 (C-8), 36.80 (C-23), 24.08 (C-24), 13.70 (C-25) ppm.

FT-IR (solid in ATR): ν 3275 s, 3250 s, 3150 m, 3020 m, 2958 s, 2930 w, 2870 w, 1665 m, 1642 m, 1599 m, 1575 m, 1540 m, 1490 vs, 1446 s, 1377 m, 1334 m, 1285 m, 1266 m, 1223 m, 1195 w, 1160 m, 1117 w, 1092 w, 1035 m, 817 m, 746 m, 684 m, 659 m cm⁻¹.

Anal. calcd. for C26H24Cl2N2OS2 (663.67): C, 62.07; H, 4.58; N, 6.33; S, 7.30%; Found: C, 62.18; H, 4.67; N, 6.33; S 7.29%.

2-((4-Chlorophenoxy)methyl)-N-(2-iso-propyl-phenylcarbamothioyl)benzamide (1c)
7.63 (dd, 1H, J = 1.4 Hz, J = 7.3 Hz, H-7), 7.60-7.52 (m, 2H, H-4, H-5), 7.49 (m, 1H, H-6), 7.34 (d, 2H, J = 9.0 Hz, H-11, H-13), 7.38-7.19 (m, 4H, H-19, H-20, H-21, H-22), 7.01 (d, 2H, J = 9.0 Hz, H-10, H-14), 5.30 (s, 2H, H-8), 2.89 (spt, 1H, J = 6.8 Hz, H-23); 1.08 (d, 6H, J = 6.8 Hz, H-24) ppm.

13C-NMR (DMSO-d6, T=298K): δ 178.66 (C-16), 169.98 (C-1), 156.95 (C-9), 140.42 (C-20), 135.36 (Cq), 135.19 (Cq), 133.23 (Cq), 124.63 (C-12), 130.99 (CH), 129.17 (C-11, C-13), 128.51 (CH), 128.31 (C-18, C-22), 128.30 (CH), 127.82 (CH), 124.02 (C-19, C-21), 116.38 (C-10, C-14), 67.73 (C-8), 34.27 (C-23), 32.98 (C-24), 21.66 (C-25), 13.69 (C-26) ppm.

FT-IR (solid in ATR): v 3153 s, 3032 m, 2957 m, 2927 m, 2860 m, 1673 s, 1583 m, 1534 vs, 1490 vs, 1411 w, 1388 m, 1267 m, 1249 s, 1157 vs, 1090 w, 1037 m, 861 w, 828 m, 776 m, 747 m, 683 m, 657 w cm⁻¹.

Anal. calcd. for C22H25ClN2O3S (453.0): C, 66.29; H, 5.56; N, 6.18; S, 7.08%; Found: C, 66.53; H, 5.79; N, 6.21; S 7.11%.

2-(4-Chlorophenoxy)methyl)-N-(2-sec-butylphenylcarbamothioyl)benzamide (Ig)

Yield 86%; mp 127.2-128.1°C.

1H-NMR (DMSO-d6, T=298K): δ 12.39 (s, 1H, NH, deuterable), 11.82 (s, 1H, NH, deuterable), 7.63 (dd, 1H, J = 1.4 Hz, J = 7.3 Hz, H-7), 7.60-7.52 (m, 2H, H-4, H-5), 7.48 (m, 1H, H-6), 7.47 (d, 2H, J = 8.5 Hz, H-18, H-22), 7.31 (d, 2H, J = 9.0 Hz, H-11, H-13), 7.21 (d, 2H, J = 8.5 Hz, H-19, H-21), 7.01 (d, 2H, J = 9.0 Hz, H-10, H-14), 5.32 (s, 2H, H-8), 2.58 (t, 2H, J = 7.3 Hz, H-23), 1.56 (q, 2H, J = 7.3 Hz, H-24), 1.33 (sxt, 2H, J = 7.3 Hz, H-25), 0.90 (t, 3H, J = 7.3 Hz, H-26) ppm.

13C-NMR (DMSO-d6, T=298K): δ 183.38 (C-16), 169.83 (C-9), 148.32 (C-20), 135.36 (Cq), 135.19 (Cq), 133.23 (Cq), 124.63 (C-12), 130.99 (CH), 129.17 (C-11, C-13), 128.51 (CH), 128.31 (C-18, C-22), 128.30 (CH), 127.82 (CH), 124.02 (C-19, C-21), 116.38 (C-10, C-14), 67.73 (C-8), 34.27 (C-23), 32.98 (C-24), 21.66 (C-25), 13.69 (C-26) ppm.

FT-IR (solid in ATR): v 3154 s, 3064 w, 3033 w, 2960 m, 2923 w, 2869 w, 1662 s, 1523 vs, 1487 vs, 1452 m, 1378 w, 1302 m, 1258 w, 1257 m, 1166 m, 1089 m, 1025 m, 1002 w, 825 m, 740 m, 665 m cm⁻¹.

Anal. calcd. for C22H25ClN2O3S (453.0): C, 66.29; H, 5.56; N, 6.18; S, 7.08%; Found: C, 65.94; H, 5.65; N, 6.11; S 7.08%.

2-(4-Chlorophenoxy)methyl)-N-(4-sec-butylphenylcarbamothioyl)benzamide (Ie)

Yield 63%; mp 113.3-114.4°C.

1H-NMR (DMSO-d6, T=298K): δ 12.38 (s, 1H, NH, deuterable), 11.81 (s, 1H, NH, deuterable), 7.63 (dd, 1H, J = 1.4 Hz, J = 7.3 Hz, H-7), 7.60-7.52 (m, 2H, H-4, H-5), 7.48 (m, 1H, H-6), 7.47 (d, 2H, J = 8.5 Hz, H-18, H-22), 7.31 (d, 2H, J = 9.0 Hz, H-11, H-13), 7.21 (d, 2H, J = 8.5 Hz, H-19, H-21), 7.01 (d, 2H, J = 9.0 Hz, H-10, H-14), 5.32 (s, 2H, H-8), 2.58 (t, 2H, J = 7.3 Hz, H-23), 1.56 (q, 2H, J = 7.3 Hz, H-24), 1.33 (sxt, 2H, J = 7.3 Hz, H-25), 0.90 (t, 3H, J = 7.3 Hz, H-26) ppm.
7.01 (d, 2H, J = 9.0 Hz, H-10, H-14), 5.32 (s, 2H, H-8); 2.61 (sxt, 1H, J = 7.2 Hz, H-23), 1.56 (qv, 2H, J = 7.2 Hz, H-25), 1.20 (d, 3H, J = 7.2 Hz, H-24), 0.78 (t, 3H, J = 7.2 Hz, H-26) ppm. 13C-NMR (DMSo-d6, T = 298K): δ 178.61 (C-16), 156.99 (C-13), 125.25 (C-18, C-22), 123.79 (C-19, C-21), 116.37 (C-10, C-14), 67.74 (C-8), 40.38 (C-23), 30.42 (C-25), 21.57 (C-24), 11.99 (C-26) ppm. FT-IR (solid in ATR): ν 3150 s, 3065 m, 3029 m, 2969 m, 2953 s, 2926 m, 2867 m, 1680 s, 1596 m, 1524 vs, 1489 vs, 1414 m, 1377 m, 1328 m, 1294 m, 1234 cm

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