ORIGINAL ARTICLE

SYNTHESIS OF SOME NEW 2-((4-CHLOROPHENOXY)METHYL)-N-(ARYLCARBAMOTHIOYL) BENZAMIDES AS POTENTIAL ANTIFUNGAL AGENTS

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Abstract

As a continuation of our previous work on the synthesis of 2-((4-chlorophenoxy)methyl)-N-(arylcarbamothioyl) benzamides and in view of the antifungal activity characterization of these molecules, we report in this paper the obtaining of new molecules having this chemical structure. The new benzamides were synthesized by reacting 2-(4-chlorophenoxymethyl)benzoyl isothiocyanate with aromatic amines in dry acetone. All the chemical structures were evaluated and characterised by ^{1}H-NMR, ^{13}C-NMR, IR spectroscopy methods and by their physical properties (melting point, solubility).

Rezumat

În continuarea cercetărilor noastre anterioare privind sinteza de 2-((4-clorofenoxi)metil)-N-(arilcarbamotioil) benzamide şi având în vedere caracterizarea activității antifungice a acestor molecule, prezentăm în această lucrare obținerea de noi molecule cu această structură chimică. Noile benzamide au fost sintetizate prin reacția izotiocianatului de 2-(4-clorofenoximetil)benzoil cu amine aromatice în acetonă anhidră. Toate structurile chimice au fost evaluate şi caracterizate prin metode spectrometrice ^{1}H-RMN, ^{13}C-RMN, IR şi prin proprietățile lor fizice (temperaturi de topire, solubilitate).

Keywords: thioureides, benzamides, ^{1}H-NMR, ^{13}C-NMR, IR spectroscopy

Introduction

Compounds bearing a thiourea moiety are challenging molecules possessing a wide spectrum of biological properties. Recent research has the aim of highlighting the use of thiourea derivatives in agriculture and pharmaco-therapy due to their biological and pharmacological activities such as herbicides [5], insecticides [4], plant growth regulatory agents [9], antibacterial [18], antifungal, antiviral [2, 17, 21], antituberculosis [8, 10], antiinflammatory [6], phenoloxidase enzymatic inhibitors [16], and antitumour agents [13].

We noticed that novel thiourea derivatives containing 1,2,4-triazole moieties were synthesized and evaluated for grow inhibition of filamentous plant pathogens fungi belonging to the genera *Colletotrichum*, *Botrytis*, *Fusarium* and *Phomopsis* using the micro-dilution broth assay. Some of these compounds showed good antifungal activity against *Phomopsis obscurans* and *P. viticola* [7].

Benzoylcarvacryl thiourea derivatives were obtained and structurally characterized. These compounds showed good antifungal activities against phytopathogenic fungi viz. *Magnaporthe grisae*, *Fusarium oxysporum*, *Dreschlera oryzae*; food spoilage yeasts viz. *Debaromyces hansenii*, *Pichia membranifaciens*; and human pathogens viz. *Candida albicans* and *Cryptococcus neoformans*. These compounds have potential applications in agriculture and medicine [19]. On the other hand thiourea derivatives are an important class of organic compounds with sulphur as ligand atom which play an important role in coordination chemistry with transition metals. The metal complexes of thiourea derivatives exhibit antimicrobial [1], antifungal [3, 15], herbicidal [20], and plant growth regulating activityies [22].

These data and also our previous research [12, 14] gave us a new area of application for these new molecules and enabled us to continue the synthesis in the thiourea derivatives seria, focused on 2-((4-chloro-phenoxy)methyl)-N-(arylcarbamothioyl)benzamides.

Materials and Methods

General experimental procedure

All chemicals were obtained from commercial suppliers (Merck Schuchardt- Hohenbrunn, Germany

and Sigma- Aldrich- Steinheim, Germany), and used without purification except ammonium thiocyanate, which was dried by heating at 100°C, acetone and 1,2-dichloroethane which were dried using calcium chloride.

TLC was performed on pre-coated plates with silica gel 60F254 (Merck).

The melting points were determined in open glass capillary with a digital apparatus (Electrothermal 9100 capillary apparatus- Bibby Scientific Ltd, Stone, UK) and are uncorrected.

Elemental analysis was obtained on a PerkinElmer 2400 Series II CHNS/O Analyzer (PerkinElmer Instruments, Shelton, USA). The values were found to be ± 0.4 % of calculated values.

The Fourier-transform infrared (FT-IR) spectra were measured on Bruker Vertex 70 FT-IR spectrometer (Bruker Optics Gmbh, Etlingen, Germany).

The NMR spectra were recorded in DMSO-d_6 on Varian Gemini 300BB instrument (Varian Medical Systems, Palo Alto, CA, USA) operating at 300.0 MHz for proton (^{1}H)-NMR, 75.0 MHz for carbon (^{13}C)-NMR, respectively. Chemical shifts were expressed in δ, parts per million (ppm), relative to tetramethylsilane used as the internal reference, and the coupling constants (*J* values) are expressed in Hertz (Hz).

The splitting patterns of ^{1}H- NMR were designated as follows: s – singlet, d – doublet, t – triplet, q – quartet, m – multiplet, b – broad, dd – doublet of doublets, dt – doublet of triplets, td – triplet of doublets. The data are reported in the following order: chemical shifts, multiplicity, and the coupling constants, number of protons and signal/atom attribution and for the ^{13}C-NMR data the order is: chemical shifts and signal/atom attribution. For ^{13}C NMR the quaternary carbon atoms are assigned as q.

The chemical shifts for hydrogen and carbon atoms were established also by 2D-NMR experiments (GCOSY, GHMBC, GHSQC).

General procedure for the preparation of ***6a- e***

Equimolar mixtures of 2-(4-chlorophenoxymethyl)-benzoyl chloride (0.01 mol) and dried ammonium thiocyanate (0.01 mol) in anhydrous acetone (20 mL) were refluxed for 1 h, and cooled at room temperature. Then, a solution of the aromatic primary amine in anhydrous acetone was added, and the reaction mixture was refluxed for 1 h. The reaction was finalized according to TCL monitoring. The new benzamides were precipitated by pouring into cold water.

Results and Discussion

As part of our interests in the new benzamides synthesis, we previously reported the synthesis of 2-(4-chlorophenoxymethyl)benzoic acid, and the preparation of the corresponding acid chloride [11].

The new benzamides **6a-e** were synthesized by reacting the not isolated 2-(4-chlorophenoxymethyl)-benzoyl isothiocyanate (**5**) with aromatic amines in dry acetone, directly added to the reaction mixture.

The isothiocyanate **5** was obtained through the reaction between 2-(4-chlorophenoxymethyl)-benzoyl chloride (**4**) and ammonium thiocyanate in dry acetone.

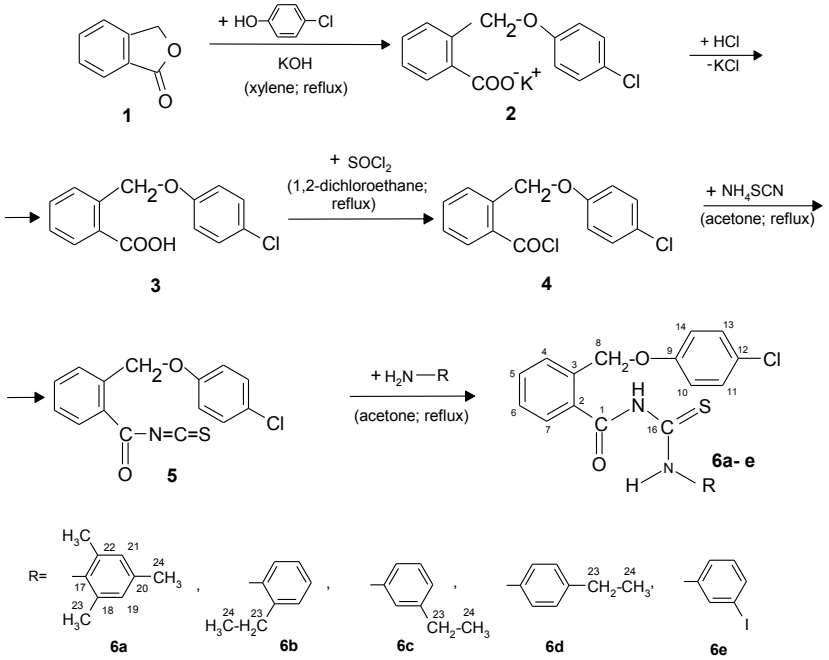

Figure 1.

The pathway for the synthesis of the new 2-((4-chlorophenoxy)methyl)-N-(arylcarbamothioyl)benzamides

Benzoyl chloride **4** was prepared by refluxing 2-(4-chlorophenoxymethyl)benzoic acid (**3**), with thionyl chloride in anhydrous 1,2-dichloroethane.

The acid **3** was prepared from phtalide (**1**) which was treated with potassium *para*-chlorophenoxide in xylene to give the potassium salt of 2-(4-chlorophenoxymethyl)benzoic acid (**2**). This was treated with hydrochloric acid solution to precipitate the acid **3**.

The new derivatives were prepared according to the scheme presented in Figure 1.

Reactions with amines were monitored by thin layer chromatography with visualization by UV-light using ethyl acetate/ cyclohexane (4:6; v/v) as solvent system.

The new compounds are soluble in cold acetone, chloroform, DMSO, DMF, hot lower alcohols, benzene, toluene, xylene and insoluble in water.

All compounds were obtained with satisfactory yields and purified by recrystallization from isopropanol.

The purity of the compounds was checked by elemental analyses.

The chemical structures were characterized by spectroscopic methods. Spectral data of the compounds were in full agreement with the proposed structures.

In the ^{1}H-NMR spectra, the N-H proton appeared as a broad singlet (**6a**) or singlet (**6b-e**) in the offset (δ, 11.77 - 12.38 ppm) region while another broad singlet (**6a**) or singlet (**6b-e**) is found in the offset (δ, 11.64 - 11.92) region. The N-H protons peaks appeared in low field which indicated that the N-H protons bonded to the substituted phenyl group form the intramolecular hydrogen bond with the oxygen atom on acyl group and form a six-member ring with other atoms in the molecule. The H-7 proton appeared at 7.62 - 7.64 ppm as a double doublet (**6a-c**), doublet (**6d**) or broad doublet (**6e**). The signals of aromatic protons H-4, H-5, H-6, H-22 appeared in a range of 7.60 - 7.42 ppm as a multiplet, excepting **6a** when H-6 proton appears as triplet of doublets. The signals of H-11 and H-13 protons are observed in the 7.33 - 7.30 ppm region and the signals of H-10 and H-14 protons were recorded at 7.01 ppm, as doublets. The signal appearing as a singlet in the aliphatic region (δ = 5.31 - 5.29 ppm) is corresponding to protons from the -CH_2- group. The ^{1}H-NMR spectrum of the compound **6a** exhibited singlets at δ 2.24 ppm, which were assigned to the H-24 and at δ 2.05 ppm for H-23. The ^{1}H-NMR spectra revealed the presence of ethyl group (**6b-d**) with characteristic quartet for H- 23 and triplet for H-24 at 2.67 - 2.46, and 1.91 - 1.05 ppm, respectively.

The ^{13}C-NMR spectra revealed peaks at δ 180.30 - 178.80 ppm for C=S and 170.31 - 169.86 ppm for C=O. Signals at δ 157.06 - 157.0 ppm reflected the presence of the C-9. ^{13}C-NMR spectra showed peaks at about δ 67.92 - 67.81 ppm for C-8. The methyl groups resonance for **6a** can be observed at δ 20.48 ppm (C-24) and 17.60 ppm (C-23). For **6b-d,** the carbon atoms resonances of the ethyl group can be found between δ 27.95 - 23.87 ppm (C-23) and 15.46 - 14.14 ppm (C-24).

The IR spectra of compounds show absorption due to the thioamide band at 3261 - 3170 cm^{-1} for νNH group. Presence of peaks in the regions 2987 - 2960cm^{-1} and 2928 - 2917 cm^{-1} indicate the existence of νC-H group from methyl and methylene groups, respectively. The peaks in the region 1660 - 1684 cm^{-1} indicate the C=O moiety. The vibration for νN–H amide group was found at 1517 - 1489 cm^{-1}. The IR spectra display absorption bands for the C=S group between 1169 - 1147 cm^{-1}. The alkyl-aryl ether bands appear at 1266 - 1232 cm^{-1}, for the antisymmetric vibration, and 1025 - 1001 cm^{-1} for the symmetric vibration.

*2-((4-Chlorophenoxy)methyl)-N-(2,4,6-trimethylphenylcarbamothioyl)benzamide (**6a**)*

yield 73%; mp 193 - 194°C.

^{1}H-NMR (dmso-d6): 11.77 (bs, 1H, NH, deuterable); 11.64 (bs, 1H, NH, deuterable); 7.64 (dd, *J* = 1.2, 7.4, 1H, H-7); 7.61 - 7.53(m, 2H, H-4, H-5); 7.48 (td, *J* = 7.4, 1H, H-6, 1.4); 7.32 (d, *J* = 9.0, 2H, H-11, H-13); 7.01 (d, *J* = 9.0, 2H, H-10, H-14); 6.89 (bs, 2H, H-19, H-21); 5.29 (s, 2H, H-8); 2.24 (s, 3H, H-24); 2.05 (s, 6H, H-23).

^{13}C-NMR (dmso-d6): 180.28 (C-16); 169.86 (C-1); 157.00 (C-9); 136.41 (Cq); 134.97 (Cq); 134.61 (C-18, C-22); 133.72 (Cq); 133.47 (Cq); 124.66 (Cq); 130.89 (CH); 129.19 (C-11, C-13); 128.88 (CH); 128.55 (CH); 128.40 (C-19, C-21); 128.01 (CH); 116.40 (C-10, C-14); 67.88 (C-8); 20.48 (C-24); 17.60 (C-23).

FT-IR (solid in ATR, ν cm^{-1}): 3172s; 3003m; 2917s; 2860w; 1684m; 1595s; 1580vs; 1489vs; 1460s; 1388vs; 1332m; 1284s; 1237s; 1168s; 1144m; 1089m; 1073m; 1049m; 1028m; 1006m; 951w; 869m; 823m; 806m; 746m; 675m; 652w.

Anal. calcd. for $C_{24}H_{23}ClN_2O_2S$ (438.97): C, 65.67; H, 5.28; N, 6.38; S, 7.3%; Found: C, 65.87; H, 5.32; N, 6.22; S 7.31%.

*2-((4-Chlorophenoxy)methyl)-N-(2-ethylphenyl-carbamothioyl)benzamide (**6b**)*

yield 69%; mp 122 - 124°C.

^{1}H-NMR (dmso-d6): 12.15 (s, 1H, NH, deuterable); 11.92 (s, 1H, NH, deuterable); 7.64 (dd, *J* = 1.2, 7.4, 1H, H-7); 7.61- 7.55 (m, 2H, H-4, H-5); 7.54-7.45 (m, 2H, H-6, H-22); 7.33 (d, *J* = 9.0, 2H, H-11, H-13); 7.31- 7.16 (m, 3H, H-19- H-21); 7.01 (d, *J* = 9.0, 2H, H-10, H-14); 5.30 (s, 2H, H-8); 2.46 (q, 2H, H-23, 7.5); 1.05 (t, 3H, H-24).

^{13}C-NMR (dmso-d6): 180.30 (C-16); 170.31 (C-1); 157.06(C-9); 138.88 (Cq); 136.07 (Cq); 135.05 (Cq); 133.54 (Cq); 124.70 (Cq); 130.96 (CH);

129.21 (C-11, C-13); 128.74 (CH); 128.64 (CH); 128.54 (CH); 127.99 (CH); 127.26 (CH); 127.12 (CH); 125.97 (CH); 116.33 (C-10, C-14); 67.92 (C-8); 23.87 (C-23); 14.14 (C-24).
FT-IR (solid in ATR, ν cm^{-1}): 3261s; 3143m; 2960s; 2928m; 2868w; 1677m; 1641m; 1582s; 1517vs; 1489vs; 1446s; 1385vs; 1300m; 1284s; 1268s; 1241s; 1145s; 1114m; 1089m; 1039m; 1017m; 1002w; 956w; 890m; 850m; 816m; 787m; 749m; 676m; 659w.
Anal. calcd. for $C_{23}H_{21}ClN_2O_2S$ (424.94): C, 65.01; H, 4.98; N, 6.59; S, 7.54%; Found: C, 65.25; H, 5.02; N, 6.44; S, 7.43%.

*2-((4-Chlorophenoxy)methyl)-N-(3-ethylphenyl-carbamothioyl)benzamide (**6c**)*

yield 64%; mp 109 - 110°C.
^{1}H-NMR (dmso-d6): 12.38 (s, 1H, NH, deuterable); 11.82 (s, 1H, NH, deuterable); 7.63 (dd, *J* = 1.2, 7.4, 1H, H-7); 7.61- 7.53 (m, 2H, H-4, H-5); 7.52-7.42 (m, 2H, H-6, H-22); 7.35 (bs, 1H, H-18); 7.31 (d, *J* = 9.0, 2H, H-11, H-13); 7.30 (t, *J* = 7.7, 1H, H-21); 7.11 (d, *J* = 7.7, 1H, H-20); 7.01 (d, *J* = 9.0, 2H, H-10, H-14); 5.31 (s, 2H, H-8); 2.67 (q, *J* = 7.5, 2H, H-23); 1.19 (t, 3H, H-24).
^{13}C-NMR (dmso-d6): 178.80 (C-16); 170.08 (C-1); 157.03 (C-9); 144.37 (Cq); 137.74 (Cq); 135.20 (Cq); 133.35 (Cq); 124.68 (Cq); 131.00 (CH); 129.20 (C-11, C-13); 128.51 (CH); 128.45 (CH); 128.41 (CH); 127.88 (CH); 125.74 (CH); 123.44 (CH); 121.55 (CH); 116.44 (C-10, C-14); 67.84 (C-8); 27.95 (C-23); 15.37 (C-24).
FT-IR (solid in ATR, ν cm^{-1}): 3147m; 3032m; 2967m; 2934m; 2876w; 1673m; 1597s; 1524vs; 1487vs; 1457s; 1381vs; 1329m; 1277s; 1240s; 1169s; 1147m; 1091m; 1070m; 1001m; 954w; 890m; 857m; 768m; 728m; 691m; 674w.
Anal. calcd. for $C_{23}H_{21}ClN_2O_2S$ (424.94): C, 65.01; H, 4.98; N, 6.59; S, 7.54%; Found: C, 65.32; H, 5.07; N, 6.47; S, 7.46%.

*2-((4-Chlorophenoxy)methyl)-N-(4-ethylphenyl-carbamothioyl)benzamide (**6d**)*

yield 81%; mp 153 - 154°C.
^{1}H-NMR (dmso-d6): 12.35 (s, 1H, NH, deuterable); 11.79 (s, 1H, NH, deuterable); 7.62 (d, 1H, H-7, 7.7); 7.60- 7.55 (m, 2H, H-4, H-5); 7.49 (m, 1H, H-6); 7.49 (d, *J* = 8.5, 2H, H-18, H-22); 7.31 (d, *J* = 9.0, 2H, H-11, H-13); 7.24 (d, *J* = 8.5, 2H, H-19, H-21); 7.01 (d, *J* = 9.0, 2H, H-10, H-14); 5.31 (s, 2H, H-8); 2.61 (q, *J* = 7.4, 2H, H-23); 1.91 (t, *J* = 7.4, 3H, H-24).
^{13}C-NMR (dmso-d6): 178.82 (C-16); 170.03(C-1); 157.01 (C-9); 141.90 (C-20); 67.81 (C-8); 27.68 (C-24); 15.46 (C-24); 135.45 (Cq); 135.23 (CH); 133.32 (Cq); 131.03 (CH); 129.22 (C-11, C-13); 128.56 (CH); 128.41 (CH); 127.86 (C-18, C-22); 124.72 (Cq); 124.20 (C-19, C-21); 124.10 (Cq); 116.46 (C-10, C-14); 67.81 (C-8); 27.68 (C-23); 15.46 (C-24).
FT-IR (solid in ATR, ν cm^{-1}): 3259s; 3032m; 2960s; 2925m; 2891w; 2866m; 1660m; 1595s; 1528vs; 1511vs; 1477vs; 1451s; 1363vs; 1311m; 1266s; 1219s; 1169s; 1116m; 1093m; 1078m; 1006m; 961w; 820m; 778m; 749m; 702m; 660w.
Anal. calcd. for $C_{23}H_{21}ClN_2O_2S$ (424.94): C, 65.01; H, 4.98; N, 6.59; S, 7.54%; Found: C, 65.12; H, 5.07; N, 6.52; S, 7.57%.

*2-((4-Chlorophenoxy)methyl)-N-(3-iodophenyl-carbamothioyl)benzamide (**6e**)*

yield 78%; mp 153 - 154°C.
^{1}H-NMR (dmso-d6): 12.34 (s, 1H, NH, deuterable); 11.88 (s, 1H, NH, deuterable); 8.05 (bs, 1H, H-18); 7.70 (dt, *J* = 7.3, 1.5, 1H, H-20); 7.62 (bd, *J* = 7.3, 1H, H-7); 7.60- 7.44 (m, 4H, H-4, H-5, H-6, H-22); 7.30 (d, *J* = 9.0, 2H, H-11, H-13); 7.20 (t, *J* = 8.1, 1H, H-21); 7.01 (d, *J* = 9.0, 2H, H-10, H-14); 5.30 (s, 2H, H-8).
^{13}C-NMR (dmso-d6): 179.07 (C-16); 169.86 (C-1); 157.02 (C-9); 142.38 (Cq); 135.29 (Cq); 134.83 (Cq); 124.77 (Cq); 93.75 (C-19); 138.61 (C-18); 136.36 (C-20); 130.17 (C-21); 129.98 (CH); 129.22 (C-11, C-13); 128.55 (CH); 128.44 (CH); 127.92 (CH); 123.87 (CH); 116.46 (C-10, C-14); 67.85 (C-8).
FT-IR(solid in ATR, ν cm^{-1}): 3360m; 3170m; 3060m; 2987s; 2966m; 1672m; 1576s; 1516vs; 1487s; 1439s; 1419s; 1383m; 1328m; 1282m; 1232s; 1147s; 1092m; 1048m; 1025m; 994w; 951w; 895m; 867w; 826m; 781w; 737m; 693m; 661w.
Anal. calcd. for $C_{21}H_{16}ClIN_2O_2S$ (522.79): C, 48.25; H, 3.08; N, 5.36; S, 6.13%; Found: C, 48.03; H, 2.97; N, 5.41; S, 6.21%.

Conclusions

Continuing our previous research in the direction of the synthesis of bioactive compounds, we have developed an efficient procedure for the synthesis of 2-((4-chlorophenoxy)methyl)-N-(arylcarbamothioyl) benzamides. Their structures were established through analyses of the spectroscopic data, confirming the synthesis and also the compounds purity. These original molecules are prone candidates for antifungal activity tests.

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