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Dedicated to the memory of
Professor Petru Spacu (1906–1995)

SYNTHESIS OF NEW 2-[2-(4-CHLOROPHENYLCARBAMOYL)-PHENOXY]ALKANOIC ACIDS DERIVATIVES

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Starting from N-(4-chlorophenyl)-2-hydroxybenzamide with ethyl α-halogenated acid esters were obtained ethyl esters of 2-[2-(4-chlorophenylcarbamoyl)-phenoxy]alkanoic acids, which were condensated with hydrazine. 2-[2-(4-Chlorophenylcarbamoyl)-phenoxy]alkanoic acids hydrazides are considered the key intermediate for the synthesis of several series of new compounds. Hydrazones were obtained by condensation of hydrazides with benzaldehyde. The compounds were characterized by physico-chemical methods (elemental analysis, FTIR, ^{1}H-NMR, ^{13}C-NMR, MS).

INTRODUCTION

The incidence of the systemic diseases as well as the spectrum of pathogens have been steadily increasing over the past few years. In spite of recent progress in the development of drugs, the treatment of infections is difficult and associated with several problems. The investigation of new compounds with a better and more selective effect and lower toxicity remains a challenge for pharmaceutical chemistry.[1]

Salicylanilides posses a wide range of biological activities, including the antimicrobial effect against a number of yeast and filamentous fungi. Substitution of phenoxiacetic acid with an electrophile group in *orto* or *para* position increases their activity against human patogenic fungi.[2-8]

Salicylamide-O-acetic hydrazide and its hydrazones obtained with substituted benzaldehydes show antiinflammatory and analgesic activity superior to salicylamide itself and lower ulcerogenic activity. [9,10]

The goal of our research is to synthesize new 2-[2-(4-chlorophenylcarbamoyl)-phenoxy]alkanoic acids ethyl esters, hydrazides and hydrazones, and to study their properties. The obtaining pathways of the synthesized compounds are presented in Scheme 1.

RESULTS AND DISCUSSION

The synthesised compounds, presented in Table 1, are white or colourless crystalline substances (needless or prisms) and were obtained with good yields 65-95%.

Yields, uncorrected melting points and spectral data of these compounds are presented in Table 2.

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Scheme 1

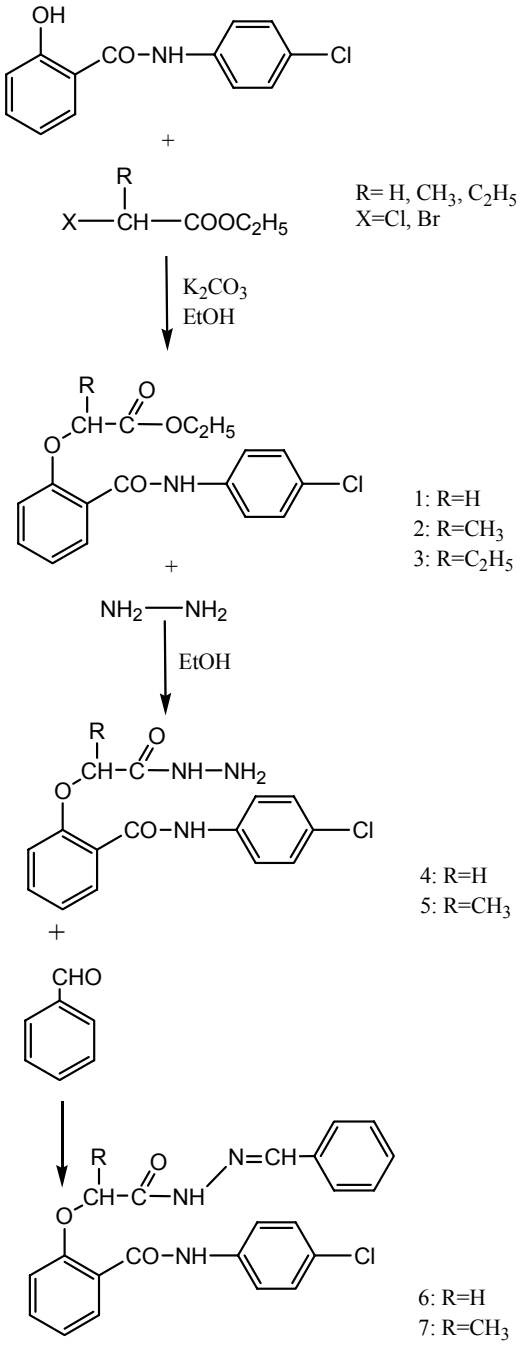

Table 1

The synthesised compounds

Comp	Compound name	R	Molecular formula/ Weight
1	2-(4-Chlorophenylcarbamoyl)-phenoxy]acetic acid ethyl ester	H	$C_{17}H_{16}NO_4Cl$ 333.61
2	2-[2-(4-Chlorophenylcarbamoyl)-phenoxy]-propionic acid ethyl ester	CH_3	$C_{18}H_{18}NO_4Cl$ 347.627
3	2-[2-(4-Chlorophenylcarbamoyl)-phenoxy]butanoic acid ethyl ester	C_2H_5	$C_{19}H_{20}NO_4Cl$ 361.644

Table 1 (continued)

4	N-(4-Chlorophenyl)-2-(hydrazinocarbonylmethoxy)-benzamide	H	$C_{15}H_{14}ClN_3O_3$ 319.07
5	N-(4-Chlorophenyl)-2-(1-hydrazinocarbonyl-ethoxy)-benzamide	CH_3	$C_{16}H_{16}ClN_3O_3$ 333.09
6	2-(Benzylidenehydrazinocarbonylmethoxy) -N-(4-chlorophenyl)-benzamide	H	$C_{22}H_{18}ClN_3O_3$ 407.10
7	2-[1-(Benzylidene-hydrazinocarbonyl)-ethoxy]-N-(4-chlorophenyl)-benzamide	CH_3	$C_{23}H_{20}ClN_3O_3$ 421.12

Table 2

Synthesised compounds characteristics

Comp	Yield %	M.p. °C	**Spectral data**
1	63	160-162	***IR***: 3430l, 3322i, 1750i, 1665i, 1550i, 1222i, 1098i, 755, 847 cm^{-1} ^{1}***H-NMR*** [δ(ppm)]: 1.19 (t, 3H, *J*=7.2, -CH_2-C$\underline{H}_3$); 4.21 (q, 2H, *J*=7.2, -C$\underline{H}_2$-CH_3); 4.96 (s, 2H, OCH_2); 7.14 (m, 2H, H_4, H_6); 7.41 (d, 2H, *J*(9,8)=8.8, H_9, H_{11}); 7.52 (t, 1H, *J*(5,6)=7.8, H_5); 7.81 (d, 2H, *J*(8,9)=8.8, H_8, H_{12}); 7.85 (d, 1H, *J*(3,4)=7.8, H_3); 10.25 (s, 1H, NH); ^{13}***C-NMR*** [δ(ppm)]: 13.74 (-CH_2-$\underline{C}H_3$); 61.00 (-$\underline{C}H_2$-CH_3); 65.56 (O$\underline{C}H_2$); 113.46 (C_6); 119.81 (C_2); 121.64 (C_4); 121.62 (C_8, C_{12}); 128.74 (C_3); 130.87 (C_9, C_{10}, C_{11}); 133.86 (C_5); 136.31 (C_7); 160.85 (C_1); 165.72 (CONH) ***MS (m/e, (relative abundance, %)):*** M^+ 333(63), 335(21); 121(100)
Comp	Yield %	M.p. °C	**Spectral data**
2	70	81-82	***IR***: 3326i, 1746i, 1660i, 1531i, 1214i, 1107i, 752, 845 cm^{-1} ^{1}***H-NMR*** [δ(ppm)]: 1.16 (t, 3H, *J*=7.2, -CH_2-C$\underline{H}_3$); 1.56 (d, 3H, *J*=7.2, OCH-C$\underline{H}_3$); 4.16 (q, 2H, *J*=7.2, C$\underline{H}_2$-CH_3); 5.20 (q, 1H, *J*=7.2, OC$\underline{H}$-CH_3); 7.11 (m, 2H, H_4, H_6); 7.40 (d, 2H, *J*(9,11)=8.4, H_9, H_{11}); 7.48 (t, 1H, *J*(5,6)=7.8, H_5); 7.75 (m, 3H, H_8, H_{12}, H_3); 10.36 (s, 1H, NH); ^{13}***C-NMR*** [δ(ppm)]: 13.66 (-CH_2-$\underline{C}H_3$); 15.54 (OCH-$\underline{C}H_3$); 59.80 (-$\underline{C}H_2$-CH_3); 80.66 (O$\underline{C}$H-CH_3); 114.06 (C_6); 119.21 (C_2); 121.63 (C_4); 121.68 (C_8, C_{12}); 128.32 (C_3); 129.97 (C_9, C_{10}, C_{11}); 133.06 (C_5); 136.88 (C_7); 160.82 (C_1); 165.52 (CONH) ***MS (m/e, (relative abundance, %)):*** M^+ 347(21), 349(9); 121(100)
3	61	54	***IR***: 3318i, 1738i, 1664i, 1530i, 1224i, 1088i, 753, 832 cm^{-1} ^{1}***H-NMR*** [δ(ppm)]: 0.96 (q, 3H, *J*=7.0, -O-CH-CH_2-C$\underline{H}_3$); 1.30 (t, 3H, *J*=7.2, -O-CH_2-C$\underline{H}_3$); 2.16 (cv, 2H, *J*=7.2, -O-CH-C$\underline{H}_2$-CH_3); 4.13 (q, 2H, *J*=7.2, -O-C$\underline{H}_2$-CH_3); 4.52 (t, 1H, *J*=6.8, -O-C$\underline{H}$-CH_2-CH_3); 7.11 (m, 2H, H_4, H_6); 7.40 (d, 2H, *J*(9,11)=8.4, H_9, H_{11}); 7.48 (t, 1H, *J*(5,6)=7.8, H_5); 7.75 (m, 3H, H_8, H_{12}, H_3); 10.35 (s, 1H, NH); ^{13}***C-NMR*** [δ(ppm)]: 7.55 (-O-CH-CH_2-$\underline{C}H_3$); 13.72 (-O-CH_2-$\underline{C}H_3$); 23.22 (-O-CH-$\underline{C}H_2$-CH_3); 59.80 (-O-$\underline{C}H_2$-CH_3); 86.65 (-O-$\underline{C}$H-CH_2-CH_3); 114.06 (C_6); 119.21 (C_2); 121.63 (C_4); 121.68 (C_8, C_{12}); 128.32 (C_3); 129.97 (C_9, C_{10}, C_{11}); 133.06 (C_5); 136.88 (C_7); 160.82 (C_1); 165.52 (CONH) ***MS (m/e, (relative abundance, %)):*** M^+ 361(33), 363(11); 121(100)
4	89	197-198	***IR***: 3331, 3275i, 1700i, 1636i, 1620i, 1547i, 1236i, 1090i, 752, 829cm^{-1} ^{1}***H-NMR*** [δ(ppm)]: 4.47 (s, 2H, OCH_2); 5.76 (s, 2H, -NH-N$\underline{H}_2$); 7.13 (m, 2H, H_5, H_3); 7.39 (m, 2H, *J*=7.7, H_9, H_{11}); 7.51 (t, 1H, *J*(5,6)=7.7, H_4); 7.76 (m, 3H, H_6, H_8, H_{12}); 9.54 (s, 1H, -CO-N$\underline{H}$-C_6H_5); 10.83 (s, 1H, -N$\underline{H}$-NH_2); ^{13}***C-NMR*** [δ(ppm)]: 77.44 (O$\underline{C}H_2$); 115.34 (C_3); 119.652 (C_1); 120.69 (C_5, C_8, C_{12}); 125.21 (C_{10}); 129.35 (C_6); 129.76 (C_9, C_{11}); 133.52 (C_4); 138.37 (C_7); 160.85 (C_2); 165.34 (-$\underline{C}$O-NH-C_6H_5); 169.99 ($\underline{C}$O-NH-NH_2); ***MS (m/e, (relative abundance, %)):*** M^+ 319(36), 321(12); 121(100)
5	68	169-170	***IR***: 3375, 3316i, 1729i, 1654i, 1597i, 1539i, 1287i, 1074i, 746, 834cm^{-1} ^{1}***H-NMR*** [δ(ppm)]: 1.47 (d, 3H, *J*=6.5, -CH-C$\underline{H}_3$); 3.29 (s, 2H, -NH-N$\underline{H}_2$); 5.08 (q, 1H, *J*=6.5, -C$\underline{H}$-CH_3); 7.11 (m, 2H, H_5, H_3); 7.41 (m, 2H, *J*(9,8)=7.7, H_9, H_{11}); 7.48 (t, 1H, *J*(5,6)=7.7, H_4); 7.67 (d, 1H, *J*(3,4)=7.8, H_6); 7.79 (d, 2H, *J*=7.8, H_8, H_{12}); 9.85 (s, 1H, -CO-N$\underline{H}$-C_6H_5); 10.29 (s, 1H, -N$\underline{H}$-NH_2) ^{13}***C-NMR*** [δ(ppm)]: 16.52 (-CH-$\underline{C}H_3$); 83.21 (-O$\underline{C}$H-); 115.38 (C_3); 119.57 (C_1); 120.57 (C_5, C_8, C_{12}); 125.29 (C_{10}); 128.75 (C_6); 129.81 (C_9, C_{11}); 134.19 (C_4); 138.29 (C_7);157.82 (C_1); 165.34 (-$\underline{C}$O-NH-C_6H_5); 174.39 ($\underline{C}$O-NH-NH_2) ***MS (m/e, (relative abundance, %)):*** M^+ 333(30), 335(10); 121(100)

Table 2 (continued)

Comp	Yield %	M.p. °C	**Spectral data**
6	96	240-243	***IR***: 3298i, 3155i, 1710i, 1700i, 1640, 1602i, 1536i, 1237i, 1096, 835, 746 cm^{-1} ***^{1}H-NMR*** [δ(ppm)]: 5.43 (s, 2H, OC<u>H</u>$_2$); 7.09 (t, 1H, *J*(4,3)=7.4, H_5); 7.15 (t, 1H, H_3); 7.35 (m, 2H, H_{14}, H_{18}); 7.48 (m, 1H, H_{16}); 7.55 (m, 1H, H_4); 7.70 (m, 2H, H_{15}, H_{17}); 7.75 (m, 2H, H_9, H_{11}); 7.81 (d, 1H, H_6); 7.97 (d, 2H, H_8, H_{12}); 8.04 (s, 1H, N=C<u>H</u>); 8.95 (s, 1H, -CO-N<u>H</u>-C_6H_5); 11.83 (s, 1H, -N<u>H</u>-N=) ***^{13}C-NMR*** [δ(ppm)]: 80.90 (-OCH_2-); 114.51 (C_3); 119.22 (C_1); 120.92 (C_5, C_8, C_{12}); 124.85 (C_{10}); 128.35 (C_6); 128.78 (C_9, C_{11}, C_{15}, C_{17}); 129.25 (C_{14}, C_{18}); 131.02 (C_{13}, C_{16});133.09 (C_4); 138.20 (C_7); 154.69 (-N=<u>C</u>H); 158.02 (C_2); 165.33 (-<u>C</u>O-NH-C_6H_5); 173.44 (-<u>C</u>O-NH-N=) ***MS (m/e, (relative abundance, %)):*** M^+ 407(33), 409(11); 121(100)
7	88	196-198	***IR***: 3381i, 3316i, 1729i, 1654, 1597i, 1539i, 1287i, 1074, 834, 746 cm^{-1} ***^{1}H-NMR*** [δ(ppm)]: 1.63 (d, 3H, -CH-C<u>H</u>$_3$); 5.49 (q, 1H, OC<u>H</u>); 7.19 (t, 1H, *J*(4,3)=7.4, H_5); 7.18 (t, 1H, H_3); 7.29 (m, 2H, H_{14}, H_{18}); 7.51 (m, 1H, H_{16}); 7.58 (m, 1H, H_4); 7.72 (m, 2H, H_{15}, H_{17}); 7.79 (m, 2H, H_9, H_{11}); 7.87 (d, 1H, H_6); 7.95 (d, 2H, H_8, H_{12}); 8.14 (s, 1H, N=C<u>H</u>); 8.97 (s, 1H, -CO-N<u>H</u>-C_6H_5); 11.85 (s, 1H, -N<u>H</u>-N=) ***^{13}C-NMR*** [δ(ppm)]: 16.52 (-CH-<u>C</u>H_3); 83.23 (-OCH-); 114.49 (C_3); 119.32 (C_1); 120.87 (C_5, C_8, C_{12}); 124.91 (C_{10}); 128.40 (C_6); 129.08 (C_9, C_{11}, C_{15}, C_{17}); 129.33 (C_{14}, C_{18}); 129.99 (C_{13}, C_{16});133.09 (C_4); 138.20 (C_7); 154.69 (-N=<u>C</u>H); 158.02 (C_2); 165.83 (-<u>C</u>O-NH-C_6H_5); 175.11 (-<u>C</u>O-NH-N=) ***MS (m/e, (relative abundance, %)):*** M^+ 421(33), 423(11); 121(100)

Table 3

Elemental analysis

Comp.	Teoretical				Found			
	%C	%H	%N	%Cl	%C	%H	%N	%Cl
1	61.18	4.83	4.20	10.62	60.84	5.07	4.17	10.59
2	62.16	5.22	4.03	10.19	61.84	5.67	4.78	10.09
3	63.07	5.57	3.87	9.80	62.84	5.77	3.78	10.00
4	56.35	4.41	13.14	11.09	55.71	4.40	12.60	10.82
5	57.58	4.83	12.59	10.62	56.18	4.64	12.11	10.20
6	64.79	4.45	10.30	8.69	64.01	3.59	9.64	9.03
7	65.48	4.78	9.96	8.40	66.23	4.82	9.47	8.02

The experimental results suggested that the ethyl esters of 2-[2-(4-chlorophenylcarbamoyl)-phenoxy]alkanoic acids derived from N-(4-chlorophenyl)-2-hydroxybenzamide were readily separated and gave pure compounds.

IR spectral data show the presence of ether bond between phenolic hydroxyl and alkyl α-C atom of ester by signals in the range 1200-1275 cm^{-1} and 1020-1075 cm^{-1}. The band characteristic for phenolic ν_{OH} is missing and between 3252-3400 cm^{-1} and 1700-1550 cm^{-1} appear characteristic signals corresponding to the vibrations of the amidic and hydrazine group.

The characterization was completed with elemental analysis, ^{1}H-NMR and ^{13}C-NMR in DMSO (the ^{1}H-NMR signal of hydrazidic group appears at 9.5 ppm, that of amidic group at 5-6 ppm and that of iminic group between 7.5-8.5 ppm; the ^{13}C-NMR signals corresponding to both carbons from hydrazidic and amidic groups appear between 161-175 ppm and those for aromatic carbons between 110-160 ppm; the base peaks in MS spectra appear at m/z=121 for all compounds, whereas for each compound two molecular peaks at M and M+2 in 3:1 ratio are found, confirming the structure).

A number of 7 compounds, N-(4-chlorophenyl)-salicylamide derivatives, not described in the literature, were synthesized and characterized. The 1:1 molar ratio for reagents gave good yields (>65%) after final purification. The purity of the compounds was higher than 95%.

The analytical methods used confirm the structure of intermediates as well as of final products. The biological activity of the compounds in this series will be tested as potentially antimicrobial compounds.

EXPERIMENTAL

Reagents and methods of analysis

Reagents: ethyl bromoacetate, ethyl chloroacetate, ethyl 2-bromopropionate, ethyl 2-bromobutyrate (Merck, for synthesis); N-(4-chlorophenyl)-salicylamide[8] (assay 98.5%); hydrazinium hydroxide (about 100% N_2H_5OH) (Merck, for synthesis); benzaldehyde (Merck, for synthesis); glacial acetic acid (Reactivul Bucureşti, for synthesis). Solvents: absolute ethanol, ethyl-methylketone, dimethylformamide, acetone (Merck, analytical purity).

Melting points were determinated with a Böetius Carl-Zeiss Jena apparatus. IR spectra in KBr pellet were recorded on Jaskow FT/IR-430 apparatus and NMR spectra were recorded in DMSO on Gemini 300 MHz instrument and internal TMS was used as reference. Mass Spectra were recorded on Varian Finnigan MAT 212 instrument, under electron impact (EI) conditions at 54 eV.

1. Synthesis of the ethyl esters **1-3**.[9] Ethyl esters of 2-[2-(4-chlorophenylcarbamoyl)-phenoxy]alkanoic acids were obtained by the reaction of N-(4-chlorophenyl)-2-hydroxybenzamide with ethyl α-halogenated acid esters in alcoholic media. A mixture of 0.05 mol N-(4-chlorophenyl)-2-hydroxybenzamide obtained according to reference **8**, and 0.05 mol K_2CO_3 anhydrous was refluxed in 50 mL absolute ethanol for 15 min. Ethyl α-halogenated acid ester was added dropwise. The optimum molar ratio was amide:ester:K_2CO_3=1:1:1. The mixture was stirred and heated on a steam bath for 10 h. The precipitated inorganic salts were filtered off and the alcoholic solution was concentrated and cooled. The separated solid was filtered, washed with water and then recrystallized from ethanol.

2. Synthesis of the hydrazides **4,5**.[9] A mixture of an ethyl ester of 2-[2-(4-chlorophenylcarbamoyl)-phenoxy]alkanoic acid (0.01 mol) and hydrazine hydrate 98% (2.2 mL,) was refluxed in 25 mL ethanol for 3 h. The reaction mixture was cooled and the separated solid was filtered, and then recrystallized from ethanol.

3. Synthesis of the hydrazones **6,7**.[9] To a solution of hydrazide 0.005 mol in 30 mL ethanol 0.005 mol of benzaldehyde were added. The reaction mixture was refluxed for 5 h. The solid formed after cooling was filtered off, washed with water and recrystallized from ethanol.

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