

Synthesis and Characterization of Some New 2-Hydroxy-N-(3-Trifluoromethyl-Phenyl)-Benzamide Derivatives

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In the reaction between 2-hydroxy-N-(3-trifluoromethyl-phenyl)-benzamide and chloro-acetic acid ethyl ester, [2-(3-trifluoromethyl-phenylcarbonyl)-phenoxy]-acetic acid ethyl ester was obtained. The ethyl ester was condensed with hydrazine giving 2-hydrazinocarbonylmethoxy-N-(3-trifluoromethyl-phenyl)-benzamide. This hydrazide is considered the key intermediate for the synthesis of new compounds. So, in the reaction between hydrazide and chloro-substituted benzaldehydes hydrazones were obtained. In order to establish their structures, all new synthesized compounds were analyzed by modern physico-chemical methods (FTIR, ¹H-NMR, ¹³C-NMR, MS).

Keywords: 2-hydroxy-N-(3-trifluoromethyl-phenyl)-benzamide derivatives, ethyl esters, hydrazides, hydrazones, salicylanilide-O-substituted

Searching for novel biological active compounds with a better and more selective effect and lower toxicity remains a challenge for the pharmaceutical chemistry.

Salicylanilides and *O*-substituted salicylanilides are a class of compounds with a broad spectrum of biological activity [1,2], including the antimicrobial effect against a number of yeast and filamentous fungi [3-9].

Salicylamide-*O*-acetic hydrazide and its hydrazones obtained with substituted benzaldehydes show anti-inflammatory and analgesic activity superior to salicylamide itself and lower ulcerogenic activity [10,11].

In order to attain such active compounds, some *ortho*-substituted phenoxyalkanoic acids and their derivatives were synthesized and characterized [12,13].

The target of this work was to synthesize some novel compounds with *o*-hydroxybenzamidic structure, derivatives with potential antibacterial and antifungal activity, and their full characterization using physico-chemical methods.

Experimental part

Reagents: ethyl chloroacetate (Aldrich, for synthesis); hydrazinium monohydrate (N₂H₄·H₂O) (Merck, for synthesis); 4-chlorobenzaldehyde, 2-chlorobenzaldehyde (Merck, for synthesis); 2-hydroxy-N-(3-trifluoromethyl-phenyl)-benzamide [9]; Solvents: absolute ethanol, ethyl-methylketone, dimethylformamide (Merck, analytical purity).

Melting points were determined with a Böetius Carl-Zeiss Jena apparatus. IR spectra in KBr pellets were recorded on a Jaskow FT/IR-430 apparatus and NMR spectra were recorded on “Bruker Avance DRX 400” instrument. Mass spectra were recorded on a high capacity ion trap, HCT Ultra PTM instrument (Bruker, Daltonics, Bremen), interfaced to a PC running the Compass™ 1.2. integrated software package, which includes the Hystar™ 3.2.37 module for instrument controlling and spectrum acquisition, Esquire Control™ 6.1.512 and Data Analysis™

3.4.179 modules for storing the ion chromatograms and processing the MS data.

The obtaining pathways of the synthesized compounds are presented in figure 1.

1. *Synthesis of the ethyl ester 1* [14]. A mixture of 0.015 mol 2-hydroxy-N-(3-trifluoromethyl-phenyl)-benzamide obtained and purified according to reference 9, and 0.015 mol anhydrous potassium carbonate was refluxed in 80 mL ethyl-methylketone. Ethyl chloroacetate (0.015 mol) was added dropwise. The optimum molar ratio was amide:ester:K₂CO₃ = 1:1:1. The mixture was stirred and heated on a steam bath for 5 h. After cooling at room temperature, the mixture was poured into water, and whirled intensively. The organic phase was separated and dried over MgSO₄. After filtration and evaporation of the solvent in vacuum, the ester was crystallized. The solid ester was recrystallized from ethanol.

2. *Synthesis of the hydrazide 2* [10]. A mixture of [2-(3-trifluoromethyl-phenylcarbonyl)-phenoxy]-acetic acid ethyl ester (0.01 mol) and hydrazine hydrate (4.5 mL) was refluxed in 30 mL ethanol for 3 h. The reaction mixture was cooled and the separated solid was filtered, then recrystallized from ethanol.

3. *Synthesis of the hydrazones 3,4* [10]. To a solution of 0.003 mol hydrazide in 30 mL ethanol, 0.003 mol of an appropriate benzaldehyde were added. The reaction mixture was refluxed for 5 h. The solid, obtained after cooling, was filtered off, washed with water and recrystallized from dimethylformamide.

Results and discussions

The synthesized compounds, presented in Table 1, are white crystalline substances (needles or prisms) and were obtained with yields ranging between 83-96%.

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

The experimental results suggest that the 2-hydroxy-N-(3-trifluoromethyl-phenyl)-benzamide derivatives were readily separated and gave pure compounds.

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Table 1
THE SYNTHESIZED COMPOUNDS

Comp. no.	Compound name	R'	Molecular formula/ Weight
1	[2-(3-Trifluoromethyl-phenylcarbamoyl)-phenoxy]-acetic acid ethyl ester	-	C ₁₈ H ₁₆ F ₃ NO ₄ 367.10
2	2-Hydrazinocarbonylmethoxy- <i>N</i> -(3-trifluoromethyl-phenyl)-benzamide	-	C ₁₆ H ₁₄ F ₃ N ₃ O ₃ 353.10
3	2-(4-Chloro-benzylidene-hydrazinocarbonylmethoxy)- <i>N</i> -(3-trifluoromethyl-phenyl)-benzamide	4-Cl	C ₂₃ H ₁₇ ClF ₃ N ₃ O ₃ 475.09
4	2-(2-Chloro-benzylidene-hydrazinocarbonylmethoxy)- <i>N</i> -(3-trifluoromethyl-phenyl)-benzamide	2-Cl	C ₂₃ H ₁₇ ClF ₃ N ₃ O ₃ 475.09

Table 2
CHARACTERIZATION OF THE SYNTHESIZED COMPOUNDS

Comp. no.	Yield (%)	M.p. (°C)	Spectral data
1	83	105-106	<p>IR v(cm⁻¹): 3328i, 3058s, 1757i, 1666i, 1600m, 1550i, 1494m, 1456s, 1436s, 1392s, 1286m, 1226i, 1170i, 1122i, 1095m, 1070m, 1020s, 783s, 756m, 709s;</p> <p>¹H-NMR [δ(ppm)]: 1.23 (t, 3H, COOCH₂CH₃); 4.24 (q, 2H, COOCH₂CH₃); 5.00 (s, 2H, OCH₂CO); 7.18 (s-t, 2H, H₃, H₅); 7.47 (d, 1H, H₁₀); 7.56 (tsc, 1H, H₁₁); 7.62 (t, 1H, H₄); 7.90 (dsc, 1H, H₁₂); 8.03 (d, 1H, H₆); 8.32 (s, 1H, H₈); 10.68 (s, 1H, CONH);</p> <p>(+)MS^I (m/z): 390.1 ([M+Na]⁺); 368.1 ([M+H]⁺);</p> <p>(+)MSⁿ (m/z): 368.1; 238.9; 224.9; 206.9; 179.0; 151.0; 121.1;</p>
2	96	166-168	<p>IR v(cm⁻¹): 3340m,l, 3288m,l, 3058s,l, 1662i, 1600m, 1558m, 1494m, 1448s, 1340i, 1288m, 1228m, 1166m, 1093s, 1072s, 1053s, 794s, 750m, 698s;</p> <p>¹H-NMR [δ(ppm)]: 4.44 (s, 2H, NH-NH₂); 4.81 (s, 2H, OCH₂CO); 7.18 (s-t, 2H, H₃, H₅); 7.47 (d, 1H, H₁₀); 7.56 (tsc, 1H, H₁₁); 7.62 (t, 1H, H₄); 7.90 (dsc, 1H, H₁₂); 8.03 (d, 1H, H₆); 8.32 (s, 1H, H₈); 9.08, 9.51 (2 isomers: cis, trans) (s, 1H, CONH-NH₂); 11.03, 11.59 (2 isomers: cis, trans) (s, 1H, CONH-Ar);</p> <p>¹³C-NMR [δ(ppm)]: 66.77 (OCH₂CO); 113.86 (C₃); 115.72 (C₈); 119.87 (C₁); 121.81 (CF₃); 123.35 (C₁₀); 124.04 (C₅); 125.48 (C₁₂); 129.65 (C₆); 129.93 (C₁₁); 130.67 (C₉); 132.91 (C₄); 139.81 (C₇); 155.26 (C₂); 164.35 (CONH-Ar); 167.14 (CONHNH₂);</p> <p>(+)MS^I (m/z): 354.1 ([M+H]⁺);</p> <p>(+)MSⁿ (m/z): 354.1; 282.0; 210.9 192.9; 165.0; 121.1;</p>

3	84	229-230	<p>IR $\nu(\text{cm}^{-1})$: 3296m, 3217s,l, 1705i, 1645i, 1600s, 1550m, 1487m, 1434m, 1340i, 1272m, 1234m, 1180m, 1163m, 1114m, 1066s, 867s, 755m, 736s, 698s, 677s, 628s, 513s, 457s;</p> <p>¹H-NMR [$\delta(\text{ppm})$]: 4.97 (s, 2H, OCH₂CO); 7.20 (t, 1H, H₅); 7.39 (d, 1H, H₃); 7.46 (d, 1H, H₁₀); 7.53 (d, 2H, H₁₅, H₁₇); 7.61 (t, 2H, H₁₁, H₄); 7.82 (d, 2H, H₁₄, H₁₈); 8.05 (d, 2H, H₆, H₁₂); 8.41 (s, 1H, H₈); 8.71 (s, 1H, -N=CH-); 10.91, 11.29 (2 isomers: cis, trans) (s, 1H, CONH-Ar); 12.03 (s, 1H, CONH-N=CH-);</p> <p>¹³C-NMR [$\delta(\text{ppm})$]: 66.53 (OCH₂CO); 114.07 (C₃); 116.12 (C₈); 119.81 (C₁); 121.65 (CF₃); 122.76 (C₁₀); 123.52 (C₅); 125.47 (C₁₂); 128.81 (C₁₅, C₁₇); 129.02 (C₆); 129.81 (C₁₁); 129.95 (C₁₃); 131.32 (C₁₄); 132.67 (C₁₈); 133.57 (C₉); 134.58 (C₄); 139.84 (C₇); 143.66 (C₁₆); 146.68 (-N=CH-); 155.76 (C₂); 163.40 (CONH-Ar); 169.73 (CONHNH=CH-);</p> <p>(+)MS¹ (m/z): 498.2 ([M+Na]⁺); 476.1 ([M+H]⁺);</p> <p>(+)MSⁿ (m/z): 476.1; 333.1; 315.0; 287.0;</p>
4	86	188-191	<p>IR $\nu(\text{cm}^{-1})$: 3352m, 3083s,l, 1701i, 1666i, 1600m, 1548s, 1488m, 1436m, 1336m, 1249m, 1228m, 1164m, 1109m, 1068s, 893s, 879m, 802s, 756m, 698s, 678s, 561s, 516s;</p> <p>¹H-NMR [$\delta(\text{ppm})$]: 4.98 (s, 2H, OCH₂CO); 7.19 (t, 1H, H₅); 7.22 (d, 1H, H₃); 7.38-7.63 (m, 4H, H₄, H₁₆, H₁₇, H₁₁); 7.87 (d, 2H, H₁₀, H₁₅); 7.98 (d, 1H, H₁₈); 8.05 (dsc, 2H, H₆, H₁₂); 8.46 (s, 1H, H₈); 8.97 (s, 1H, -N=CH-); 10.90, 11.27 (2 isomers: cis, trans) (s, 1H, CONH-Ar); 12.05, 12.14 (2 isomers: cis, trans) (s, 1H, CONH-N=CH-);</p> <p>¹³C-NMR [$\delta(\text{ppm})$]: 66.55 (OCH₂CO); 114.06 (C₃); 116.14 (C₈); 119.83 (C₁); 121.67 (CF₃); 122.77 (C₁₀); 123.52 (C₅); 125.49 (C₁₂); 127.23 (C₁₇); 127.54 (C₆); 129.83 (C₁₁, C₁₅); 130.98 (C₁₈); 131.32 (C₉); 131.57 (C₁₃); 133.08 (C₁₆); 133.57 (C₄); 134.63 (C₁₄); 139.83 (C₁₇); 140.94 (-N=CH-); 155.74 (C₂); 163.41 (CONH-Ar); 169.82 (CONHNH=CH-);</p> <p>(+)MS¹ (m/z): 498.2 ([M+Na]⁺); 476.1 ([M+H]⁺);</p> <p>(+)MSⁿ (m/z): 476.1; 333.0; 315.0; 287.0; 216.9; 177.9; 121.0;</p>

IR spectral data of the ethyl ester show the presence of an ether bond between phenolic hydroxyl and alkyl α -C atom of the ester by signals at 1226 cm^{-1} ($\nu^{\text{as}}\text{COC aromatic}$) and 1122 cm^{-1} ($\nu^{\text{as}}\text{COC alifatic}$). The carbonyl group of the ester ($\nu\text{C=O}$) appears at 1757 cm^{-1} , but in the IR spectra of the hydrazide this band is missing, proving the conversion of the ester into hydrazide. The signals corresponding to

the vibrations of the amidic and hydrazidic group appear between $3290\text{--}3360\text{ cm}^{-1}$ (νNH) and $1660\text{--}1710\text{ cm}^{-1}$ ($\nu\text{C=O}$).

The obtained compounds were also analyzed by ¹H-NMR in DMSO and ¹³C-NMR in CCl₄. In order to facilitate the NMR data interpretation, in figure 2, the numbering of the aromatic rings is presented. The ¹H-NMR shifts of ethyl

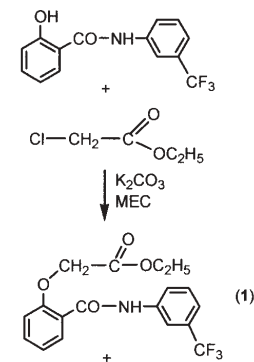
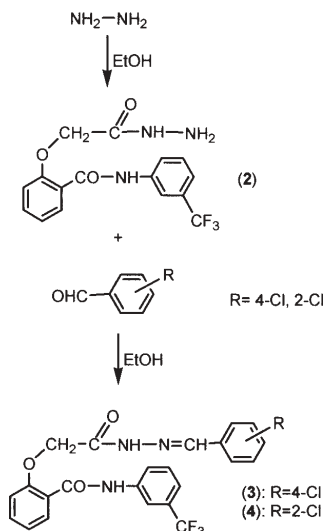


Fig. 1. The obtaining pathways of the synthesized compounds



group from ester appear between 1.2-4.3 ppm, that of the amidic group between 10.6-11.6 ppm, that of hydrazidic group, from both, hydrazides and hydrazones, between 9.0-12.2 ppm, and that of iminic group between 8.7-8.9 ppm. The ^{13}C -NMR signals corresponding to both carbons from the hydrazidic and amidic groups appear between 163-170 ppm and those for the aromatic carbons between 113-156 ppm.

In order to obtain a full characterization of the synthesized compounds, MS analysis, using positive electrospray ionization (+ESI) technique, was performed. The compounds were dissolved in pure methanol, and both, $+MS^1$ and tandem mass spectra $+MS^n$ ($n=2-6$), were acquired. The MS^1 revealed the presence only of the peaks corresponding to the protonated and/or sodiated molecular ions: $[M+H]^+$ and $[M+Na]^+$, whereas the fragmentation spectra clearly proved their structure.

Conclusions

A number of 4 novel 2-hydroxy-*N*-(3-trifluoromethylphenyl)-benzamide derivatives were synthesized using

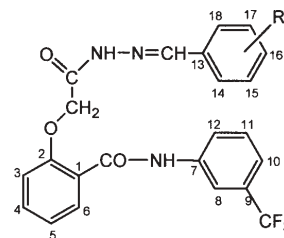


Fig. 2. Numbering of the aromatic rings

adapted literature methods and their characterization by spectral methods was performed.

The 1:1 molar ratio for the reagents in the synthesis of hydrazones gave good yields (>83%) after the final purification.

The employed analytical methods confirm the identity and structure of all investigated compounds.

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