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SYNTHESIS AND CHARACTERIZATION OF SOME NEW 5-BROMO-2-HYDROXY-BENZAMIDE DERIVATIVES

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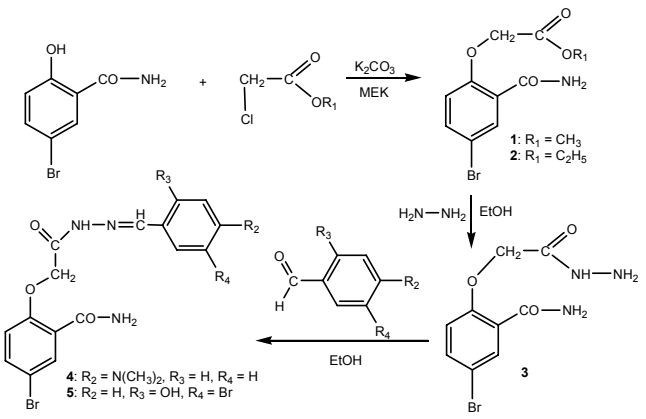
Compounds with 2-hydroxy-benzamide structure are well known for their biological activity. Thus, synthesizing the derivatives of this moiety without its side effects has been a constant challenge for the medicinal chemistry. Consequently, we considered worthwhile to synthesize some 5-bromo-salicylamide derivatives which might possess enhanced biological activity. Starting from 5-bromo-2-hydroxy-benzamide and methyl/ethyl α-halogenated acid esters were obtained methyl/ethyl esters, which in reaction with hydrazine provide hydrazides. In the next step, hydrazides were condensated with substituted benzaldehydes, obtaining hydrazones. In order to assess the structural identity of the synthesized compounds, modern physico-chemical methods (FTIR, ^{1}H-NMR, ^{13}C-NMR, MS) were employed. For all analyzed compounds, the obtained data proved their identity and provide their elemental composition.



INTRODUCTION

The consequence of an improper and excessive use of antibiotics, among other reasons, consists in the appearance of pathogenic bacterial strains that are extremely resistant to most available antibiotics.[1] Moreover, the incidence of disease and the action spectrum of pathogens are constantly increasing. So, finding novel biologically active compounds, able to defeat such resistant organisms, represents a challenge for researchers.[2,3]

Salicylamides (2-hydroxy-benzamides) and their derivatives are used in various pharmaceutical and biochemical fields, due to their antifungal, antibacterial, antimycobacterial, analgesic, antiinflammatory properties.[4-7]

Usually, the antimicrobial activity of salicylamide esters is similar or higher than the one of amide itself.[8] Hydrazides and hydrazones represent two important classes of biologically active compounds possessing among antimicrobial activity, analgesic, antiinflammatory, anticonvulsant, antitubercular and antitumoral activities.[9] Salicylamidoacetic acid hydrazide revealed higher antiinflammatory and analgesic activity and lower ulcerogenic activity, compared

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to salicylamide.[8] Isonicotinic acid hydrazide and its hydrazones possess high activity against *M. tuberculosis*.[10] Some hydrazones were reported to be less toxic than the related hydrazides due to the blockage of amino group.[11]

Thus, attempting to combine these properties in order to improve the biological activity, minimizing the toxicity, side effects simultaneously, some new molecules, 5-bromo-2-hydroxy-benzamide derivatives, were obtained by substitution of the phenolic hydrogen with alkoxycarbonylalkyl, hydrazinocarbonylalkyl and benzylidene-hydrazinocarbonylalkyl and characterized.

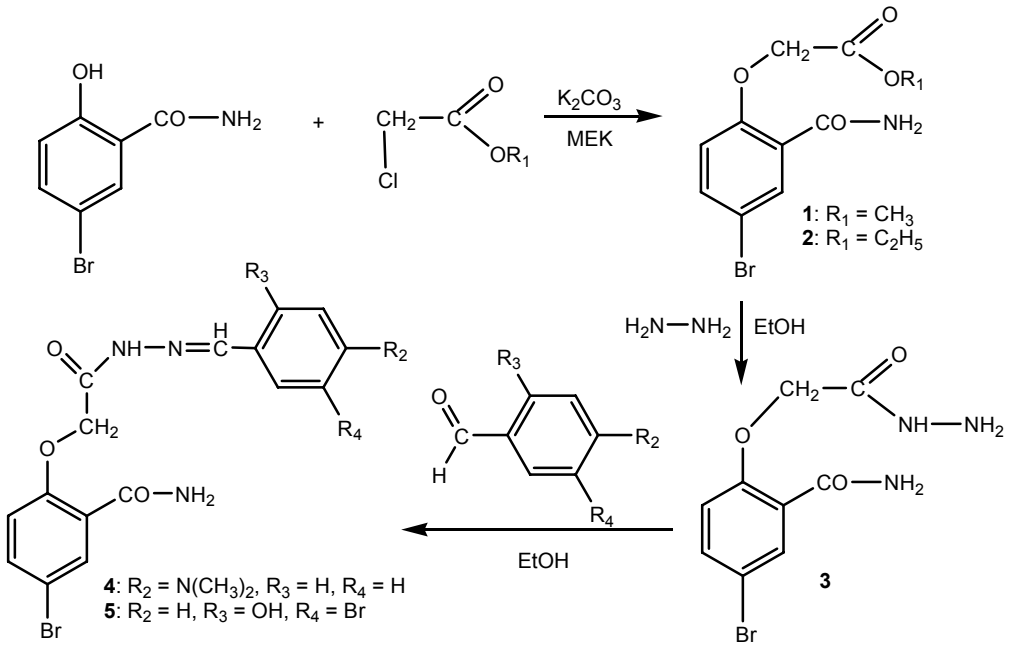
RESULTS AND DISCUSSION

The titled compounds, 2-hydroxy-benzamide derivatives, are presented in Table 1, along with some characteristics (melting point, yield). The synthesized compounds (**1**-**5**) are white, grey, crystalline substances, needles or prisms. The synthetic route for preparation of the target compounds is outlined in Scheme 1. Simple crystallization from absolute ethanol or dimethylformamide was used for final purification; the desired compounds were obtained in yields between 50-96%. The lowest reaction yield was obtained in case of the methyl ester (**1**), but this compound was still used for obtaining hydrazides, in order to establish its behavior in the reaction. The hydrazide (**2**), either got from methyl ester or ethyl ester, was obtained with similar yields and spectral characteristics.

Table 1

Titled compounds characteristics

No.	Compound name	Molecular formula / weight	M.p. (ºC)	Yield (%)
1	(4-Bromo-2-carbamoyl-phenoxy)-acetic acid methyl ester	$C_{10}H_{10}BrNO_4$ 288.09	157-162	50
2	(4-Bromo-2-carbamoyl-phenoxy)-acetic acid ethyl ester	$C_{11}H_{12}BrNO_4$ 302.12	130-133	70
3	5-Bromo-2-hydrazinocarbonylmethoxy-benzamide	$C_9H_{10}BrN_3O_3$ 288.10	205-207	78
4	5-Bromo-2-(4-dimethylamino-benzylidene-hydrazinocarbonylmethoxy)-benzamide	$C_{18}H_{19}BrN_4O_3$ 419.27	225-228	95
5	2-[1-(5-Bromo-2-hydroxy-benzylidene-hydrazinocarbonyl)-ethoxy]-5-chloro-N-phenyl-benzamide	$C_{16}H_{13}Br_2N_3O_4$ 471.10	250-255	96



Scheme 1 – The reaction pathways of the 5-bromo-salicylamide derivatives.

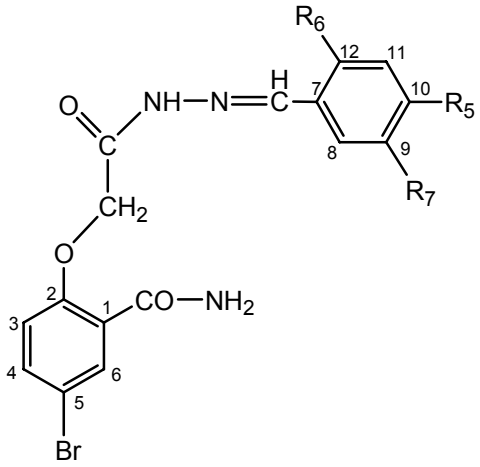


Fig. 1 – Numbering of aromatic rings.

The structures of the synthesized compounds were elucidated by IR, ^{1}H-NMR, ^{13}C-NMR and MS analysis. In order to facilitate the NMR spectra interpretation, the numbering of the aromatic rings is presented in Fig. 1.

The IR spectral data of the esters show the existence of an ether bond between the phenolic hydroxyl group and the alkyl α-C atom of the ester by signals in the range 1210–1230 and 1070–1080 cm^{-1}. The carbonyl groups from the esters appear in the range 1740–1750 cm^{-1}; however, in the IR spectra of the hydrazides, this band is absent, which indicates the formation of the hydrazide. The vibrations of the amide and hydrazide group appear as signals between 3150–3400 and 1630–1660 cm^{-1}, respectively.

The ^{1}H-NMR shifts of the methyl protons from the methyl ester were observed in the spectra as singlet at δ = 3.74, whereas the ethyl group from the ethyl ester appears between 1.2 and 4.3 ppm. These signals are completely absent in hydrazide spectra, which is a spectral evidence of the ester conversion into the hydrazide. The protons of the amide group, in all analyzed compounds, were observed as singlets between 7.7 and 8.2 ppm. The observation of two distinct signals for amide protons can be explained by hindered rotation of the C-N bond in the amide moiety, which is typical of amides. The hydrazide group, from both hydrazides and hydrazones, appears between 9.4 and 11.8 ppm and the imine group between 8.2 and 8.6 ppm.

The ^{13}C-NMR signals corresponding to the carbons from the amide and hydrazide groups appear in the range 164–169 ppm and those of the aromatic carbons between 111 and 156 ppm.

MS[1] and mass calculation revealed the presence of the molecular ions corresponding to monoprotonated molecules, $[M+H]^+$, and/or species exhibiting sodiated and potassiated adducts $[M+Na]^+$ and $[M+K]^+$. Fine and detailed structural analyses were performed by multistage mass spectrometry **MS^n** (n=2-4), the obtained multistage sequencing data clearly confirmed the structure of the synthesized compounds.

EXPERIMENTAL

1. Chemicals and equipment

Reagents: ethyl chloroacetate, methyl chloroacetate, 5-bromo-2-hydroxy-benzamide (Aldrich, for synthesis); hydrazine monohydrate ($N_2H_4 \cdot H_2O$) (Merck, for synthesis); 4-dimethylaminobenzaldehyde, 5-bromosalicylaldehyde (Merck, for synthesis). Solvents: absolute ethanol, dimethylformamide, 2-butanone (Merck, analytical purity). Commercial grade reagents were used as supplied.

Melting points are uncorrected and measured using Böetius Carl-Zeiss Jena apparatus. IR spectra (ν_{max} in cm^{-1}) were recorded as KBr pellet, on a Jaskow FTIR-430 instrument. The ^{1}H, ^{13}C-NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ on a Bruker Avance DRX 400 spectrometer, operating at 400 MHz. Chemical shifts (δ values) are expressed in ppm against tetramethylsilane (TMS) as internal standard and coupling constants (*J*) are reported in Hz. Mass spectra were obtained in methanol on a high capacity ion trap, Bruker HCT Ultra PTM instrument, using positive electrospray ionization (+ESI) technique.

2. Synthesis

2.1. Methyl/ethyl esters.[11] To a mixture of appropriate salicylamide and anhydrous K_2CO_3, refluxed in 2-butanone, ethyl/methylchloro-acetate was added dropwise. Optimum molar ratio was amide:ester:K_2CO_3 = 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 shaken intensively. The organic phase was dried over $MgSO_4$. After filtration and evaporation of solvent in vacuum, the esters (1,2) were obtained in crystalline form and were recrystallized from absolute ethanol.

2.2. Hydrazides.[12] A mixture of methyl/ethyl ester and hydrazine hydrate was refluxed in ethanol for 3 h. The reaction mixture was cooled, the separated solid filtered off, then subjected to recrystallization from absolute ethanol.

2.3. Hydrazones.[12] To a solution of hydrazide in ethanol, the appropriate benzaldehyde was added. The reaction mixture was refluxed for 5 h. The solid obtained after cooling was filtered off, washed with water and recrystallized from dimethylformamide.

The spectral data of the synthesized compounds are listed below.

(4-Bromo-2-carbamoyl-phenoxy)-acetic acid methyl ester **(1)**
IR ν(cm^{-1}) KBr pellet: 3400; 3170; 1750; 1650; 1595; 1560; 1490; 1430; 1415; 1350; 1250; 1210; 1130; 1076; 820; 790;
^{1}H-NMR [δ(ppm)]: 3.74 (s, 3H, COOC$\underline{H}_3$); 4.99 (s, 2H, OC$\underline{H}_2$CO); 7.10 (d, 1H, H_3, *J*=8.8); 7.64 (d_{sc}, 1H, H_4, *J*=8.8); 7.81 (s, 1H$_6$); 7.98 (s_{sc}, 2H, CON$\underline{H}_2$);
^{13}C-NMR [δ(ppm)]: 52.13 (COO$\underline{C}H_3$); 65.64 (O$\underline{C}H_2$CO); 112.96 (C_5); 115.98 (C_3); 124.54 (C_1); 133.31 (C_6); 134.92 (C_4); 154.88 (C_2); 164.33 ($\underline{C}$ONH); 168.94 ($\underline{C}$OOCH$_3$);
(+)MS^1 (m/z): 325.5 ([M+K]$^+$); 309.5 ([M+Na]$^+$); 287.5 ([M+H]$^+$);
(+)MS^n (m/z): 288.5; 270.4; 242.4;

(4-Bromo-2-carbamoyl-phenoxy)-acetic acid ethyl ester **(2)**
IR ν(cm^{-1}) KBr pellet: 3399; 3150; 1740; 1650; 1590; 1560; 1500; 1450; 1410; 1340; 1270; 1230; 1140; 1075; 860; 850;
^{1}H-NMR [δ(ppm)]: 1.24 (t, 3H, COOCH$_2$C$\underline{H}_3$, *J*=8.0); 4.21 (q, 2H, COO$\underline{C}H_2$CH$_3$, *J*=8.0); 4.97 (s, 2H, O$\underline{C}H_2$COO); 7.10 (d, 1H, H_3, *J*=8.8); 7.65 (d_{sc}, 1H, H_4, *J*=8.8); 7.83 (s, 1H, H_6); 7.98 (s_{sc}, 2H, CON$\underline{H}_2$);
^{13}C-NMR [δ(ppm)]: 13.97 (COOCH$_2$$\underline{C}H_3$); 61.09 (COO$\underline{C}H_2CH_3$); 65.75 (O$\underline{C}H_2$CO); 112.92 ($C_5$); 116.01 ($C_3$); 124.45 ($C_1$); 133.32 ($C_6$); 134.95 ($C_4$); 154.91 ($C_2$); 164.27 ($\underline{C}$ONH); 168.38 ($\underline{C}$OOCH$_2CH_3$);
(+)MS^1 (m/z): 339.6 ([M+K]$^+$); 323.6 ([M+Na]$^+$); 301.5 ([M+H]$^+$);
(+)MS^n (m/z): 302.5; 284.5; 256.5; 230.4;

5-Bromo-2-hydrazinocarbonylmethoxy-benzamide **(3)**
IR ν(cm^{-1}) KBr pellet: 3310; 3340; 1652; 1630; 1600; 1556; 1500; 1270; 1235; 1100; 1040; 820; 795;
^{1}H-NMR [δ(ppm)]: 4.37 (s, 2H, NH-$\underline{N}H_2$); 4.71 (s, 2H, O$\underline{C}H_2$CO); 7.05 (d, 1H, H_3, *J*=8.8); 7.63 (d_{sc}, 1H, H_4, *J*=8.8); 7.75, 8.15 (2s, 2H, CON$\underline{H}_2$) (2 conformers: cis, trans); 7.84 (s_{sc}, 2H, H_6); 9.49 (s, 1H, CON$\underline{H}$-NH$_2$);
^{13}C-NMR [δ(ppm)]: 67.19 (O$\underline{C}$H$_2$CO); 112.88 (C_5); 116.20 (C_3); 126.04 (C_1); 132.77 (C_6); 134.63 (C_4); 155.07 (C_2); 165.39 ($\underline{C}$ONH$_2$); 166.65 ($\underline{C}$ONHNH$_2$);
(+)MS^1 (m/z): 287.2 ([M+H]$^+$);
(+)MS^n (m/z): 287.3; 270.3; 245.3; 214.9; 199.1; 134.1; 106.3

5-Bromo-2-(4-dimethylamino-benzylidene-hydrazinocarbonylmethoxy)-benzamide **(4)**
IR ν(cm^{-1}) KBr pellet: 3440; 3170; 1680; 1620; 1590; 1530; 1480; 1420; 1260; 1210; 1100; 1055; 820; 735;
^{1}H-NMR [δ(ppm)]: 2.97 (s, 6H, N($\underline{C}$H$_3$)$_2$); 5.30 (s, 2H, O$\underline{C}$H$_2$CO); 6.74 (d, 2H, H_9, H_{11}, *J*=8.4); 7.20 (d, 1H, H_3, *J*=8.8), 7.55 (d, 2H, H_8, H_{12}, *J*=8.4); 7.66 (d, 1H, H_4, *J*=8.8); 7.79, 8.03 (2s, 2H, CON$\underline{H}_2$); 7.91 (s, 1H, H_6); 8.51 (s, 1H, -N=$\underline{C}$H-); 11.49, 11.58 (2 conformers: cis, trans) (s, 1H, CON$\underline{H}$-N=CH-);
^{13}C-NMR [δ(ppm)]: 38.89-40.14 (N($\underline{C}$H$_3$)$_2$); 66.43 (O$\underline{C}$H$_2$CO); 111.69 (C_9, C_{11}); 112.59 (C_5); 116.29 (C_3); 121.14 (C_7); 124.27 (C_1); 128.37 (C_8, C_{12}); 133.40 (C_6); 135.06 (C_4); 145.37 (C_{10}); 151.48 (-N=$\underline{C}$H-); 155.64 (C_2); 164.37 ($\underline{C}$ONH$_2$); 168.24 ($\underline{C}$ONH-N=CH-);
(+)MS^1 (m/z): 418.6 ([M+H]$^+$);
(+)MS^n (m/z): 418.5; 401.4; 175.3; 146.3;

5-Bromo-2-(5-bromo-2-hydroxy-benzylidene-hydrazinocarbonylmethoxy)-benzamide **(5)**
IR n(cm^{-1}) KBr pellet: 3612, 3417, 1689, 1649, 1585, 1477, 1419, 1301, 1269, 1066, 877, 802
^{1}H-NMR [d(ppm)]: 4.92 (s, 1H, OH); 5.38 (s, 2H, OCH$_2$CO); 6.88 (d, 1H, H_3, *J*=8.8), 7.22 (d, 1H, H_{11}, *J*=8.8); 7.41 (d_{sc}, 1H, H_{10}, *J*=8.8); 7.67 (d_{sc}, 1H, H_4, *J*=8.8); 7.77, 8.00 (2 conformers: cis, trans) (2s, 2H, CONH$_2$); 7.87 (s_{sc}, 1H, H_8); 7.92 (s, 1H, H_6); 8.29 (s, 1H, -N=$\underline{C}$H); 10.38, 11.75 (2 conformers: cis, trans) (s, 1H, CON$\underline{H}$-N=CH-);
^{13}C-NMR [d(ppm)]: 66.42 (O$\underline{C}$H$_2$CO); 112.61 (C_5); 116.44 (C_3, C_9); 118.37 (C_{11}); 122.37 (C_7); 124.36 (C_1); 127.96 (C_6); 133.33 (C_8); 133.63 (C_{10}); 135.01 (C_4); 140.04 (-N=$\underline{C}$H-); 155.58 (C_{12}); 155.64 (C_2); 164.42 ($\underline{C}$ONH$_2$); 168.88 ($\underline{C}$ONH-N=CH-);
(+)MS^1 (m/z): 470.7 ([M+H]$^+$);
(+)MS^n (m/z): 470.5; 454.2; 426.2; 397.3; 226.0; 197.9.

CONCLUSIONS

A number of 5 novel compounds, 5-bromo-2-hydroxy-benzamide derivatives, were synthesized in order to enlarge the collection of potential biologically active compounds.

The titled compounds belonging to esters, hydrazides and hydrazones classes were obtained with good yields (>50%) and a full characterization of them, using modern analytical methods, was achieved.

The attained spectral data proved the identity and provided the elemental composition of all analyzed compounds.

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