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SYNTHESIS AND CHARACTERIZATION OF SOME NEW 5-CHLORO-2-HYDROXY-N-PHENYLBENZAMIDE DERIVATIVES

Ioana M.C. IENAŞCU,[a,b] Raluca O. POP,[c] Adina CĂTA,[a*] Mariana N. ŞTEFĂNUŢ[a] and Iuliana M. POPESCU[d]

[a] National Institute of Research and Development for Electrochemistry and Condensed Matter, 144 Dr. A. P. Podeanu, 300569, Timişoara, Roumania, adina.cata@yahoo.com
[b] "Vasile Goldiş" Western University of Arad, Faculty of Pharmacy, Department of Pharmaceutical Sciences, 86 Liviu Rebreanu, 310045, Arad, Roumania
[c] "Victor Babeş" University of Medicine and Pharmacy Timişoara, Faculty of Pharmacy, 2 Eftimie Murgu Square, 300041, Timişoara, Roumania
[d] Banat's Agricultural Science University, Faculty of Agriculture, Department of Chemistry and Biochemistry, 119 Calea Aradului, 300645, Timişoara, Roumania

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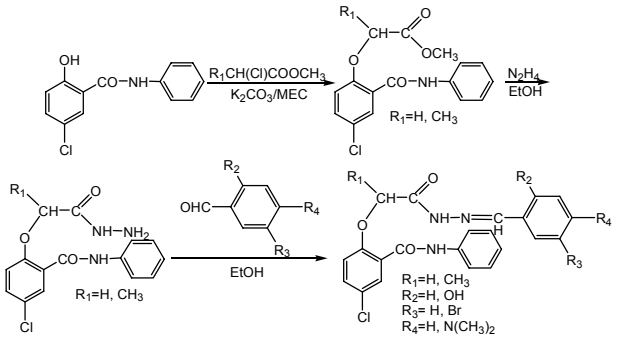
There has been significant interest in the development of new compounds possessing an azometine group (NHN=CH-) due to their varied potential biological activities. With the purpose of obtaining novel compounds with a wide spectrum of pharmaceutical applications, the synthesis of 5-chloro-2-hydroxy-N-phenylbenzamide methyl esters, hydrazides and hydrazones was achieved. The synthesized compounds are crystalline substances whose purification required simple crystallization from absolute ethanol or dimethylformamide. The methyl esters were obtained in yields between 48-65%, while, for the hydrazides and hydrazones higher yields were obtained (84-96%). Useful tools, FTIR, ^{1}H-NMR, ^{13}C-NMR, MS, were used to identify and to characterize the synthetized compounds.



INTRODUCTION

The increasing number of microbial infections underlines the importance of developing new chemotherapeutics with antimicrobial effects. One common disease, tuberculosis, lethal in several cases, is caused by several strains of mycobacteria. The treatment of this disease is facilitated by the use of different antimicrobial chemotherapeutics, the substantial application of these drugs being an important reason of increased antibiotic resistance among bacteria. Additionally, the antibiotic resistance of methicillin/vancomycin-resistant *Staphylococcus aureus* became one of the most challenging global health problems that cause dangerous nosocomial infections in the community with high levels of morbidity and mortality.[1,2] These problems present also economic consequences, therefore novel, effective antibacterial drugs are needed.

Many salicylanilide ester derivatives have been demonstrated an effective and encouraging treatment against pathogenic fungi and bacteria, including strains like methicillin-resistant *Staphylococcus aureus* and isoniazid-resistant mycobacteria which are resistant to at least one clinically used drugs.[3]

* Corresponding author: adina.cata@yahoo.com

Hydrazide-hydrazones have been demonstrated to possess, antimicrobial, antitubercular, analgesic, anticonvulsant, antiinflammatory, antiplatelet and antitumoral activities.[4-6]

In this study, a series of salicylanilide esters, hydrazides and hydrazones, with potential biological properties, were synthesized and characterized.

RESULTS AND DISCUSSION

Starting from 5-chloro-2-hydroxy-N-phenylbenzamide, methyl esters, hydrazides and hydrazones, were obtained. Molecular formula/weight, melting points and yields are presented in Table 1. The synthesized compounds (**1-8**) are white/yellow, crystalline substances, needles or prisms. Scheme 1 presents the synthetic route for preparation of the title compounds. The esters and hydrazides were purified by re- crystallization from absolute ethanol and the hydrazones from dimethylformamide. After the final purification, the compounds were obtained in yields between 48-96%. The hydrazides (**3**, **4**) were obtained previously, from ethyl esters in higher yields,[7] but the spectral characteristics were similar, so the data obtained from IR, NMR and MS, for these two compounds are not presented herein.

IR, ^{1}H-NMR, ^{13}C-NMR and MS analysis were used to confirm the structures of the synthesized derivatives. The numbering of the aromatic rings needed for the NMR spectra interpretation is presented in Figure 1.

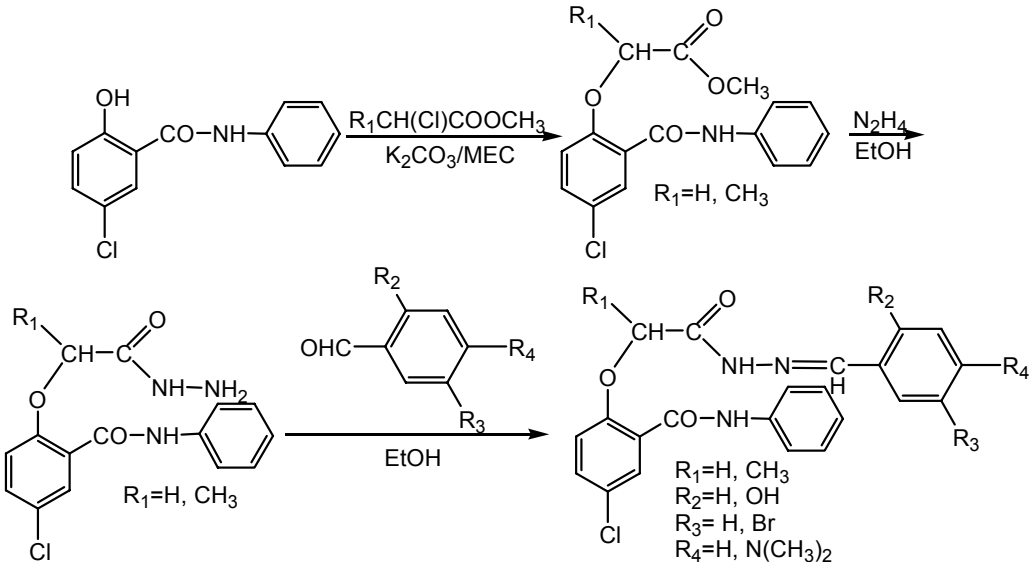
The infrared spectra of the esters exhibited the presence of absorption bands in the range 1210–1230 and 1040–1110 cm^{-1}, corresponding to the formation of an ether bond between the phenolic hydroxyl group and the alkyl α-C atom of the ester. The carbonyl groups from the esters appear at 1765 cm^{-1}, both for methyl and ethyl ester. The signals corresponding to the vibrations of the amide and hydrazide group appear between 3180–3370 and 1630–1670 cm^{-1}.

The ^{1}H-NMR spectra of the esters showed characteristic signals in the region 3.7-3.8 ppm corresponding to the methyl group. The amide protons are present in all the compounds and are verified by the appearance of singlets between 10.3 and 11.1 ppm. The hydrazide group from hydrazones appears as signal between 11.4 and 12.2 ppm and the azomethine group between 7.9 and 8.6 ppm. Two distinct signals for amide and hydrazide protons can be generally observed, due to the hindered rotation of the C-N link in the amide moiety.

Table 1

Titled compounds characteristics

No.	Compound name	Molecular formula/weight	M.p. (ºC)	Yield (%)
1	(4-Chloro-2-phenylcarbamoyl-phenoxy)-acetic acid methyl ester	$C_{16}H_{14}ClNO_4$ 319.74	195-196	65
2	2-(4-Chloro-2-phenylcarbamoyl-phenoxy)-propionic acid methyl ester	$C_{17}H_{16}ClNO_4$ 333.77	127-128	48
3	5-Chloro-2-hydrazinocarbonyl-methoxy-N-phenyl-benzamide	$C_{15}H_{14}ClN_3O_3$ 319.07	194-196	89
4	5-Chloro-2-(1-hydrazinocarbonyl-ethoxy)-N-phenyl-benzamide	$C_{16}H_{16}ClN_3O_3$ 333.09	208-210	87
5	5-Chloro-2-(4-dimethylamino-benzylidene-hydrazinocarbonyl-methoxy)-N-phenyl-benzamide	$C_{24}H_{23}ClN_4O_3$ 450.92	220-222	96
6	5-Chloro-2-[1-(4-dimethylamino-benzylidene-hydrazinocarbonyl)-ethoxy]-N-phenyl-benzamide	$C_{25}H_{25}ClN_4O_3$ 464.94	193-195	84
7	2-(5-Bromo-2-hydroxy-benzylidene-hydrazinocarbonyl-methoxy)-5-chloro-N-phenyl-benzamide	$C_{22}H_{17}BrClN_3O_4$ 502.75	240-243	88
8	2-[1-(5-Bromo-2-hydroxy-benzylidene-hydrazinocarbonyl)-ethoxy]-5-chloro-N-phenyl-benzamide	$C_{23}H_{19}BrClN_3O_4$ 516.77	222-225	90



Scheme 1 – Synthesis of the 5-chloro-salicylanilide derivatives.

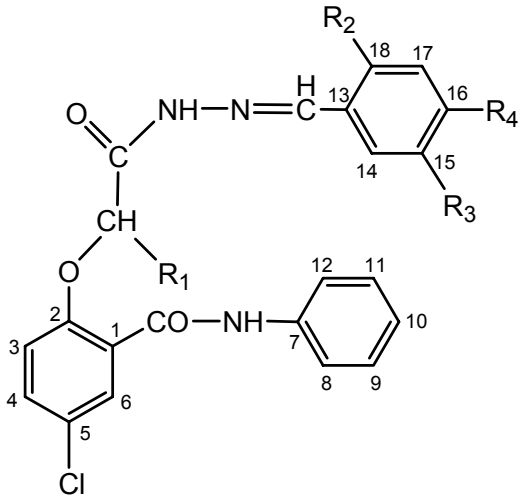


Fig. 1 – Numbering of aromatic rings.

The ^{13}***C-NMR*** spectroscopic studies also confirmed the formation of all synthesized compounds. Thus, the signals corresponding to the carbons from the hydrazide and amide groups appear in the range 161–170 ppm. The aromatic carbons showed signals in the range 110-157 ppm.

The (-) nanoESI QTOF MS screening and mass calculation revealed the presence of the molecular ions corresponding to monodeprotonated molecules, $[M\text{-}H^+]^-$. Due to the presence of chlorine and bromine in the molecules of the synthesized compounds, MS screening spectra revealed the presence of the corresponding isotopes. ***The (-) nanoESI QTOF MS/MS*** fragmentation mass spectra were performed by collision induced dissociation (CID) at low energies, the obtained sequencing data offered the detailed structural analyses of the synthesized compounds.

EXPERIMENTAL

1. Chemicals and Equipment

The reagents used for synthesis are: methyl chloroacetate, 5-chloro-2-hydroxy-N-phenylbenzamide (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 Stuart Melting Point SMP30 apparatus. IR spectra (ν_{max} in cm^{-1}) were recorded as KBr pellet, on a Bruker Vertex 70 FTIR 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 in ppm) are expressed against tetramethylsilane (TMS) as internal standard and coupling constants (*J*) are reported in Hz. Mass spectra were obtained in methanol on a hybrid QTOF micro (Micromass/Waters, Manchester, UK) instrument, using negative ion mode. All samples were submitted to (−) nanoESI QTOF MS and MS/MS analysis by collision induced dissociation (CID) at low energies.

2. Synthesis

2.1. *Methyl esters* (**1**,**2**).[7,8] To a mixture of 5-chloro-2-hydroxy-N-phenylbenzamide and anhydrous K_2CO_3, refluxed in 2-butanone, 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 were obtained in crystalline form and were recrystallized from absolute ethanol.

2.2. *Hydrazides* (**3**,**4**).[7,9] A mixture of methyl 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* (**5-8**). [7,9] To a solution of hydrazide in ethanol, the corresponding 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-Chloro-2-phenylcarbamoyl-phenoxy)-acetic acid methyl ester* (1)**

IR ν(cm^{-1}) KBr pellet: 3340, 1765, 1660, 1605, 1550, 1499, 1440, 1370, 1320, 1260, 1210, 1148, 1110, 1070, 1040, 1000, 870, 760, 770, 750, 510;

^{1}H-NMR [δ(ppm)]: 3.78 (s, 3H, COOC$\underline{H}_3$); 5.02 (s, 2H, O$\underline{CH}_2$CO); 7.14 (t, 1H, H_{10}, *J*=7.6); 7.25 (d, 1H, H_3, *J*=8.8); 7.38 (t, 2H, H_9, H_{11} *J*=8.0); 7.56 (d_{sc}, 1H, H_4, *J*=8.8); 7.80 (d, 2H, H_8, H_{12}, *J*=8.0); 7.87 (s_{sc}, 1H, H_6); 10.30 (s, 1H, CON$\underline{H}$);

^{13}C-NMR [δ(ppm)]: 51.93 (COO$\underline{C}$H$_3$); 65.99 (O$\underline{C}$H$_2$CO); 115.61 (C_3); 119.90 (C_8, C_{12}); 123.70 (C_1); 124.99 (C_{10}); 125.53 (C_5); 128.48 (C_9, C_{11}); 129.81 (C_6); 131.86 (C_4); 138.40 (C_7); 153.73 (C_2); 161.60 (C=O); 168.70 (C=O);

(-)MS (m/z): 319.28, 319.33, 319.54, 320.40, 320.45, 320.55, 321.55, 321.65, 321.70;

(-)MS/MS (m/z): 319.54, 287.34, 247.13, 227.10, 168.81, 153.60, 93.40;

***2-(4-Chloro-2-phenylcarbamoyl-phenoxy)-propionic acid methyl ester* (2)**

IR ν(cm^{-1}) KBr pellet: 3365, 2960, 1765, 1649, 1605, 1552, 1500, 1440, 1370, 1300, 1280, 1222, 1150, 1110, 1049, 990, 940, 820, 750, 710, 649, 510, 420;

^{1}H-NMR [δ(ppm)]: 1.59 (d, 3H, OCH(C$\underline{H}_3$)CO, *J*=6.8); 3.74 (s, 3H, COOC$\underline{H}_3$); 5.28 (q, 1H, OC$\underline{H}$(CH$_3$)CO, *J*=6.8); 7.13 \(t, 1H, H_{10}, *J*=7.6); 7.21 (d, 1H, H_3, *J*=8.8); 7.38 (t, 2H, H_9, H_{11}, *J*=8.0); 7.55 (d_{sc}, 1H, H_4, *J*=8.8); 7.76 (d, 2H, H_8, H_{12}, *J*=8.0); 7.77 (s, 1H, H_6); 10.30 (s, 1H, CON$\underline{H}$);

^{13}C-NMR [δ(ppm)]: 17.94 (OCH(C$\underline{H}_3$)CO); 52.54 (COO$\underline{C}$H$_3$); 73.36 (O$\underline{C}$H(CH$_3$)CO); 116.22 (C_3); 119.64 (C_8, C_{12}); 123.84 (C_1); 125.58 (C_{10}); 126.48 (C_5); 128.85 (C_9, C_{11}); 129.80 (C_6); 131.81 (C_4); 138.68 (C_7); 153.29 (C_2); 162.26 (C=O); 171.86 (C=O);

(-)MS (m/z): 333.38, 333.47, 333.58, 334.61, 334.65, 334.76, 334.77, 335.58, 335.65, 335.69;

(-)MS/MS (m/z): 333.58, 301.40, 247.14, 240.10, 181.83, 153.68, 93.42

***5-Chloro-2-(4-dimethylamino-benzylidene-hydrazinocarbonylmethoxy)-N-phenyl-benzamide* (5)**

IR ν(cm^{-1}) KBr pellet: 3340, 3200, 1700, 1650, 1603, 1540, 1480, 1438, 1264, 1230, 1090, 820, 740, 720, 655, 530;

^{1}H-NMR [δ(ppm)]: 2.97 (s, 6H, -N(C$\underline{H}_3$)$_2$); 5.40 (s, 2H, O$\underline{CH}_2$CO); 6.74 (d, 3H, H_3, H_{15}, H_{17}, *J*=8.8); 7.13 (t, 1H, H_{10}, *J*=7.2); 7.38 (t, 2H, H_9, H_{11}, *J*=8.8); 7.57 (d, 2H, H_{14}, H_{18}, *J*=8.8); 7.62 (d_{sc}, 1H, H_4, *J*=8.8); 7.92 (s, 1H, -N=C$\underline{H}$-); 7.95 (s, 1H, H_6); 7.96 (d, 2H, H_8, H_{12}, *J*=8.8); 10.72, 11.06 (2 conformers: *cis*, *trans*) (s, 1H, CON$\underline{H}$-Ar); 11.46, 11.66 (2 conformers: *cis*, *trans*) (s, 1H, CON$\underline{H}$-N=);

^{13}C-NMR [δ(ppm)]: 38.89-40.14 (N(C$\underline{H}_3$)$_2$); 66.88 (O$\underline{C}$H$_2$CO); 111.64 (C_{15}, C_{17}); 116.27 (C_3); 120.06 (C_8, C_{12}); 121.02 (C_1); 123.78 (C_{13}); 124.40 (C_{10}); 125.51 (C_5); 128.43 (C_{14}, C_{18}); 128.68 (C_6, C_9, C_{11}); 132.52 (C_4); 138.93 (C_7); 145.75 (C_{16}); 151.50 (-N=$\underline{C}$H-); 154.51 (C_2); 161.65 (C=O); 168.75 (C=O);

(-)MS (m/z): 450.96, 452.97;

(-)MS/MS (m/z): 452.99, 333.52, 319.42, 288.24, 260.14, 249.08, 231.01, 150.67, 120.56, 92.39;

***5-Chloro-2-[1-(4-dimethylamino-benzylidene-hydrazinocarbonyl)-ethoxy]-N-phenyl-benzamide* (6)**

IR ν(cm^{-1}) KBr pellet: 3360, 3280, 1700, 1670, 1620, 1600, 1550, 1500, 1480, 1260, 1230, 1060, 810, 770, 700, 666, 540;

^{1}H-NMR [δ(ppm)]: 1.63 (d_{sc}, 3H, OCH(C$\underline{H}_3$)CO, *J*=6.4); 2.98 (s, 6H, -N(C$\underline{H}_3$)$_2$); 5.22 (q, 1H, OC$\underline{H}$(CH$_3$)CO, *J*=6.4); 6.75 (t, 2H, H_9, H_{11}, *J*=8.8); 7.13 (t, 1H, H_{10}, *J*=7.2); 7.29 (d_{sc}, 1H, H_3, *J*=8.8); 7.37-7.42 (m, 2H, H_{15}, H_{17}); 7.51 (d, 1H, H_4, *J*=8.8); 7.55-7.60 (m, 2H, H_{14}, H_{18}); 7.81 (d, 2H, H_8, H_{12}, *J*=8.4); 7.95 (s, 1H, -N=C$\underline{H}$-); 8.12 (s, 1H, H_6); 10.78, 11.01 (2 conformers: *cis*, *trans*) (s, 1H, CON$\underline{H}$-Ar); 11.63 (s, 1H, CON$\underline{H}$-N=);

^{13}C-NMR [δ(ppm)]: 17.77 (OCH(C$\underline{H}_3$)CO); 38.89-40.14 (N(C$\underline{H}_3$)$_2$); 72.24 (O$\underline{C}$H(CH$_3$)CO); 111.71 (C_{15}, C_{17}); 116.72 (C_3); 119.46 (C_8, C_{12}); 120.96 (C_1); 123.88 (C_{13}); 125.94 (C_{10}); 127.31 (C_5); 128.67 (C_{14}, C_{18}); 128.94 (C_6, C_9, C_{11}); 131.94 (C_4); 138.81 (C_7); 146.41 (C_{16}); 149.68 (-N=$\underline{C}$H-); 153.57 (C_2); 162.81 (C=O); 167.18 (C=O);

(-)MS (m/z): 464.92, 465.05, 467.07, 468.077;

(-)MS/MS (m/z): 467.13, 347.71, 319.54, 301.44, 275.33, 249.17, 183.83, 164.81, 153.69, 120.59, 92.43;

***2-(5-Bromo-2-hydroxy-benzylidene-hydrazinocarbonylmethoxy)-5-chloro-N-phenyl-benzamide* (7)**

IR ν(cm^{-1}) KBr pellet: 3842, 3747, 3676, 3309, 3149, 3070, 2983, 1704, 1633, 1595, 1539, 1483, 1448, 1402, 1272, 1230, 1186, 1149, 1114, 1072, 960, 916, 800, 756, 725, 675, 567, 543, 505, 472, 430;

^{1}H-NMR [δ(ppm)]: 4.98 (s, 1H, OH); 5.49 (s, 2H, O$\underline{CH}_2$CO); 6.89 (d, 1H, H_3, *J*=8.8), 7.13 (t, 1H, H_{10}, *J*=7.2); 7.36-7.45 (m, 4H, H_9, H_{11}, H_{16}, H_{17}); 7.63 (d_{sc}, 1H, H_4, *J*=8.8); 7.91 (s, 1H, H_{14}); 7.93 (s, 1H, H_6); 7.96 (d, 2H, H_8, H_{12}, *J*=8.8); 8.31 (s, 1H, -N=C$\underline{H}$-); 10.61, 10.97 (2 conformers: *cis*, *trans*) (CO-N$\underline{H}$-Ar); 11.91, 12.04 (2 conformers: *cis*, *trans*) (s, 1H, CON$\underline{H}$-N=);

^{13}C-NMR [δ(ppm)]: 66.91 (O$\underline{C}$H$_2$CO); 110.88 (C_3); 116.47 (C_{15}); 118.37 (C_{17}); 119.94 (C_1); 120.03 (C_8, C_{12}); 122.27 (C_{13}); 123.80 (C_{10}); 125.51 (C_5); 127.96 (C_6); 128.69 (C_9, C_{11}); 129.75 (C_4); 132.09 (C_{14}); 132.47 (C_{16}); 138.84 (C_7); 140.36 (-N=$\underline{C}$H-); 154.56 (C_{18}); 155.69 (C_2); 161.72 (C=O); 169.44 (C=O);

(-)MS (m/z): 502.37, 504.36, 506.43, 507.47;

(-)MS/MS (m/z): 504.45, 412.87, 328.50, 288.41, 249.18, 228.99, 212.95, 198.85, 172.80, 153.69, 128.59, 89.39;

***2-[1-(5-Bromo-2-hydroxy-benzylidene-hydrazinocarbonyl)-ethoxy]-5-chloro-N-phenyl-benzamide* (8)**

IR ν(cm^{-1}) KBr pellet: 3842, 3747, 3649, 3182, 3049, 2983, 1878, 1691, 1631, 1602, 1550, 1475, 1442, 1396, 1353, 1326,

1269, 1232, 1122, 1037, 962, 929, 891, 846, 817, 757, 727, 688, 651, 551, 507, 478, 441;
^{1}H-NMR [δ(ppm)]: 1.64 (d_{sc}, 3H, OCH(CH_3)CO); 5.22 (s, 1H, OH); 6.12 (s, 2H, OCH(CH_3)CO); 6.90 (d, 1H, H_3, *J*=8.8), 7.14 (t, 1H, H_{10}, *J*=7.2); 7.36-7.44 (m, 3H, H_9, H_{11}, H_{17}); 7.58 (d_{sc}, 1H, H_{16}, *J*=8.8); 7.75-7.82 (m, 3H, H_4, H_6, H_{14}); 7.96 (d, 2H, H_8, H_{12}, *J*=8.8); 8.53 (s, 1H, -N=CH-); 10.62, 10.92 (2 conformers: *cis*, *trans*) (CO-NH-Ar); 11.88, 12.14 (2 conformers: *cis*, *trans*) (s, 1H, CONH-N=);
^{13}C-NMR [δ(ppm)]: 17.83 (OCH(CH_3)CO); 74.51 (OCH(CH_3)CO); 110.53 (C_3); 116.62 (C_{15}); 118.61 (C_{17}); 119.56 (C_8, C_{12}); 121.24 (C_1); 123.91 (C_{13}); 125.84 (C_{10}); 127.14 (C_5); 128.89 (C_6, C_9, C_{11}); 129.68 (C_4); 131.93 (C_{14}); 133.92 (C_{16}); 138.71 (C_7); 145.77 (-N=CH-); 153.34 (C_2); 156.29 (C_{18}); 162.95 (CONH-Ar); 167.68 (CONH-N=);
(-)MS (m/z): 516.45, 518.44, 520.43, 507.48;
(-)MS/MS (m/z): 518.38, 398.84, 318.59, 300.52, 270.29, 247.22, 198.87, 170.80, 128.59.

CONCLUSIONS

Eight 5-chloro-salicylanilide derivatives, esters, hydrazides and hydrazones, were prepared in high yield and purity. Except the hydrazides (**3**,**4**), the rest of compounds were for the first time obtained during these experiments, extending the collection of potential biologically active substances.

The synthesized compounds were also characterized, using modern techniques, such as IR, NMR and MS. All spectral data brought useful information on the structure of newly synthesized compounds, proving their identity.

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