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Article

Crystal Structure of the 5-Chloro Salicylamides: Three Different Types of the H-bonding Influenced Linear Chain Formation in the Solid State

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Abstract: Three *N*-substituted 5-chlorosalicylamides (4-chlorophenyl, **2a**; benzyl, **2b**; phenethyl **2c**) differing in the length of the 'linker' between the benzene ring and the amide moiety were prepared in order to compare their supramolecular architecture. The intramolecular NH ··O(H) hydrogen bond and the intermolecular C=O ··H–O hydrogen bond were found in the crystal structure of **2a** and **2c** thus forming an infinite linear chain. Compound **2b** had a different arrangement with the intramolecular C=O ··H–O hydrogen bond and another intermolecular NH ··O(H) hydrogen forming a linear infinite chain.

Keywords: salicylic amides; X-ray; H-bond; microwave synthesis

1. Introduction

N-substituted hydroxy benzamides (salicylanilides) have been reported as pharmacological compounds with numerous biological activities. *N*-Phenyl and *N*-benzyl salicylamides were investigated for their antimicrobial [1], antifungal [2], and various antiviral properties [3]. These compounds were also used as topical antimycotics and antiplaque [4], molluscicidal [5] and anthelmentic agents [6].

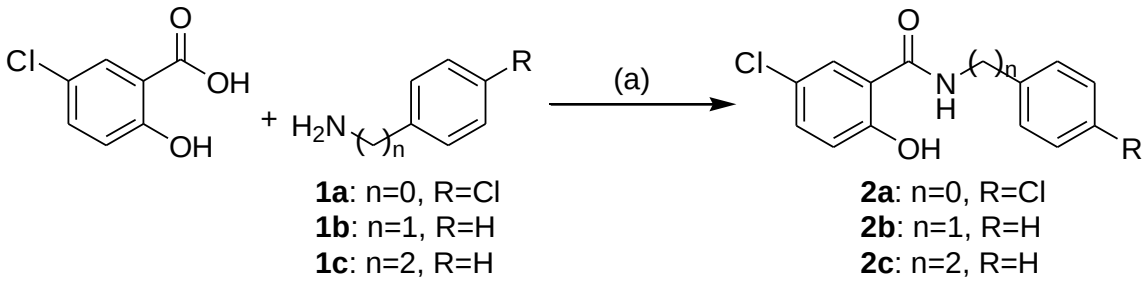
Although the antibacterial activity involves multiple mechanisms, these compounds have been shown to be inhibitors of the two-component regulatory systems (TCS) of bacteria [7–9]. The most recent studies identified them as selective inhibitors of interleukin-12p40 production [10,11] and inhibitors of the protein kinase epidermal growth factor receptor (EGFR PTK) [12] as well as cell permeable inhibitors of poly(ADP-ribose) glycohydrolase (PARG) [13].

The classical approach for the synthesis of *N*-substituted 2-hydroxybenzamides is based on the refluxing of substituted salicylic acid with appropriate amine (aniline, benzylamine, phenethylamine) in chlorobenzene in the presence of phosphorus trichloride for several hours [14,15]. Other synthetic approaches were also reported [16] as microwave assisted synthesis, which reduced total reaction time from several hours to minutes with comparable yields [17].

2. Results and Discussion

During our research that focused on the antimycobacterial properties of salicylanilide derivatives, we prepared their various *O*-substituted derivatives such as acetates [18], *N*-protected amino acid esters [19,20] and carbamates [21]. The preparation of the starting salicylanilides was a routine step of the synthetic pathway. Several approaches were tested from which the microwave-assisted synthesis seemed to be optimal (Scheme 1). This procedure is quick and products can be isolated in high yields. Simple crystallization from absolute ethanol is usually used for final purification of the desired salicylamides.

Scheme 1. Microwave-assisted synthesis of studied salicylamides.



1a: n=0, R=Cl
1b: n=1, R=H
1c: n=2, R=H

2a: n=0, R=Cl
2b: n=1, R=H
2c: n=2, R=H

Reagents and conditions: (a) = MW irradiation 400 W, PCl_3, chlorobenzene, reflux 20 min.

In the next study, we focused on investigating the comparison of crystal structures of three different amides of 5-chlorosalicylic acid, namely 5-chloro-2-hydroxy-*N*-(4-chlorophenyl)benzamide (**2a**), 5-chloro-2-hydroxy-*N*-benzylbenzamide (**2b**) and 5-chloro-2-hydroxy-*N*-phenethylbenzamide (**2c**) whose selected structural parameters are summarized in Tables 1 and 2.

Table 1. Selected interatomic distances [Å], angles and torsion angles [º].

	2a	**2b**	**2c**
C1-C7	1.494(3)	1.490(2)	1.489(4)
C7-O1	1.239(3)	1.250(2)	1.244(3)
C7-N1	1.343(3)	1.331(2)	1.330(3)
N1-C8	1.413(3)	1.463(2)	1.446(3)
C2-O2	1.362(3)	1.355(2)	1.356(3)
C5-Cl1	1.742(2)	1.7427(18)	1.744(3)
C1-C7-N1	117.58(19)	118.46(15)	118.8(2)
O1-C7-N1	122.0(2)	121.88(16)	119.6(2)
C7-N1-C8	128.26(19)	123.04(15)	122.2(2)
C2-C1-C7-O1	1.87	13.92	3.54

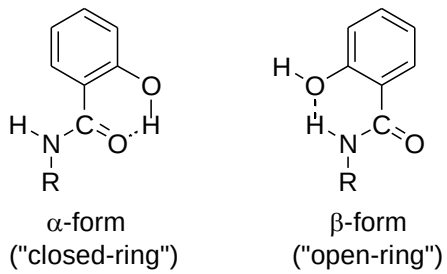
Table 2. Hydrogen bonds for **2a-c** [Å, °].

	D-H ··A	d(D-H)	d(H ··A)	d(D ··A)	<(DAH)	symm. transformation
2a	N1 H1 O2	0.86	1.93	2.651(2)	141.0	─
	O2 H2 O1	0.82	1.79	2.607(2)	174.7	−x, 1/2 + y, 1/2 − z
2b	N(1)-H(1) ··O(2)	0.86	2.14	2.898(2)	146.4	−x, + y, 1/2 − z
	O(2)-H(2) ··O(1)	0.82	1.78	2.5166(19)	148.0	─
2c	N(1)-H(1) ··O(2)	0.86	1.95	2.638(3)	136.2	─
	O(2)-H(2) ··O(1)	0.82	1.77	2.582(2)	169.2	+ x, - y, 1/2 + z

2.1. Crystal Structure Determination

As early as 1961, Tamura *et al*. suggested [22] that polymorphism observed in the crystals of most amides is related to the varied types of molecular arrangement connected by different types of hydrogen bonds. It is also known that the molecules of salicylamides and their thioanalogues can exist in at least two possible configurations due to both intramolecular and intermolecular hydrogen bonds. These two configurations are occasionally labeled as α- and β-form [23], rotameric forms or "open-ring" and "closed-ring" tautomers [24,25] (Figure 1)

Figure 1. Rotameric forms of salicylamides.



Sometimes *s-cis* and *s-trans* conformers of the α-form are distinguished [26] although according to IUPAC recommendations from 1996 [27] such prefixes should not be applied to *N*-substituted amides (*E*/*Z*-convention is correct). It is widely believed [25] that "closed-ring" tautomers, which are thermodynamically favorable in solution for parent salicylamide [28] as well as for substituted

salicylanilides [25,26], are responsible for their inhibition activity mentioned in the introduction. However the situation is completely different in the solid phase. Regardless of substitution on both aromatic rings, all known salicylanilides [29–39] exclusively exist in the "open-ring" β-form. If two stable polymorphs exist [32], then they differ only in their packing patterns and not in their hydrogen bonds patterns.

In the case of compound **2a** where the *p*-chlorophenyl ring is directly attached to the amide nitrogen atom the molecule is nearly planar (dihedral angle between both benzene rings is only 4.96 °) with the intramolecular NH···O(H) bond between the amide and hydroxy groups (Figure 2) thus forming an "open-ring" β-form. Another type of the H-bond (Table 2) present within the molecule is the intermolecular contact between the hydroxy group and the C=O group of the adjacent molecule which is perpendicularly oriented towards the first molecule thus forming an infinite linear chain in the solid state (Figure 3). All bond lengths and angles (see Table 1) in **2a** are in the usual ranges reported in the literature [40]. The structure comparison of **2a** with the series of reported salicylanilides [29-39] shows only some small changes mainly in the degree of planarity of compounds and the intramolecular architecture driven by the differences in the types of H-bonding.

Figure 2. The ORTEP view of **2a** at 50% probability level.

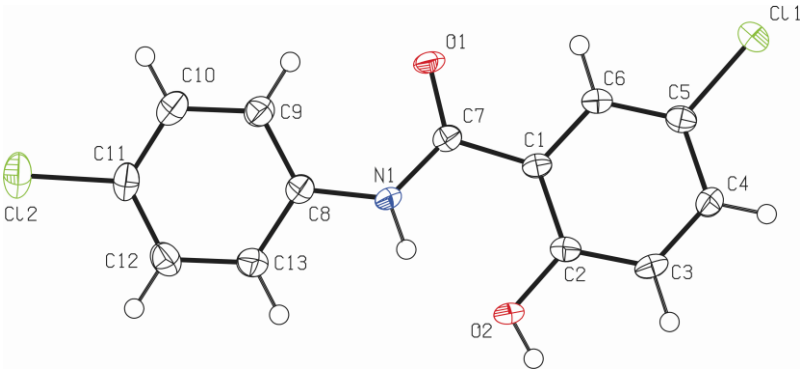
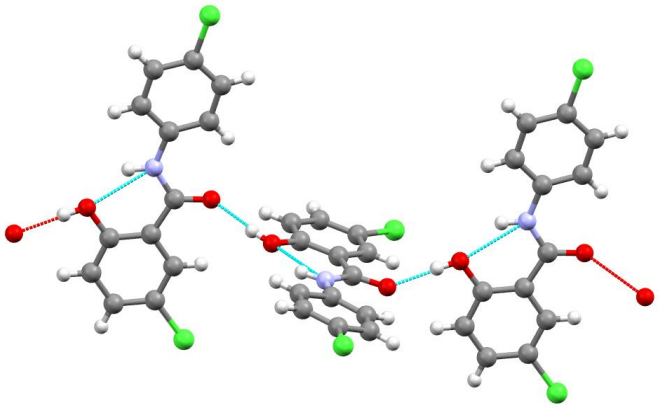


Figure 3. Packing pattern showing intermolecular H-bonding interactions found in the structure of **2a**.



The second compound **2b** containing a methylene linker between the amide nitrogen and the benzene ring is no longer planar but has a bent shape (Figure 4) due to the impossibility of delocalization of a nitrogen lone electron pair into the benzene ring resulting from lack of electronic coupling, and broken by the methylene spacer with saturated bonds. However, the main difference

between structures **2a** and **2b** (except the shape of the molecule) lies in a different type of the hydrogen bond in the molecule. The compound **2b** has a "closed-ring" arrangement with an intramolecular hydrogen bond between the carbonyl oxygen atom and the hydroxy group (C=O ··H–O) similarly as it was observed for *N*-benzyl-2-hydroxybenzamide [41], *N*-(3-pyridylmethyl)-2-hydroxybenzamide [42] and even for 2-hydroxy-*N*-methylbenzamide [43]. Another intermolecular NH ··O(H) bond between the amide and the hydroxy group of **2b** then forms a linear infinite chain in which all molecules have the same orientation (Figure 5).

Figure 4. The ORTEP view of **2b** at 50% probability level.

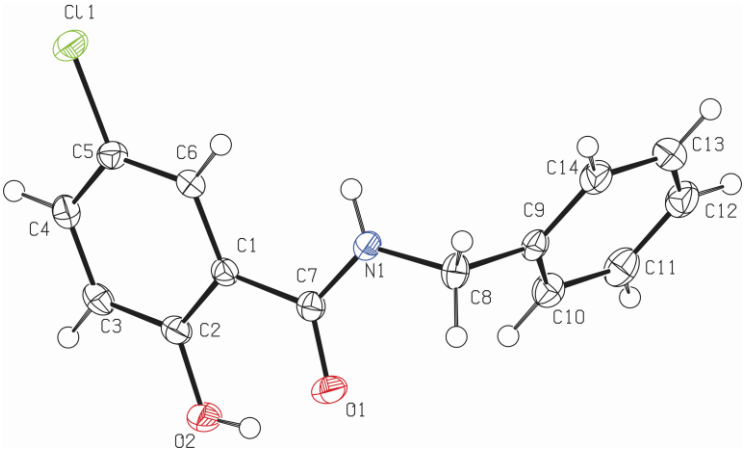
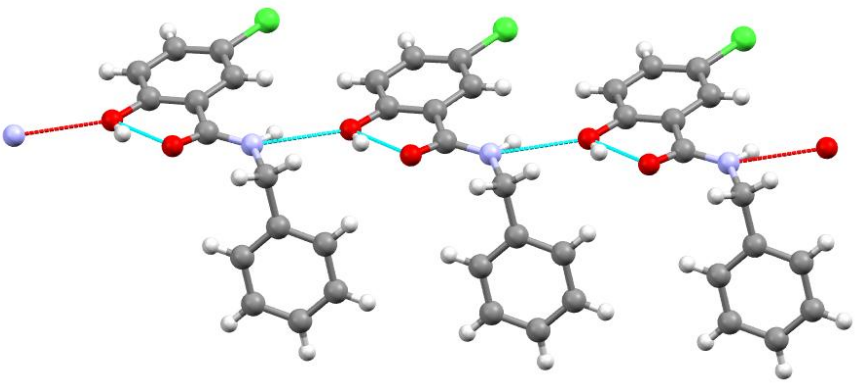


Figure 5. Packing pattern showing intermolecular H-bonding interactions found in the structure of **2b**.

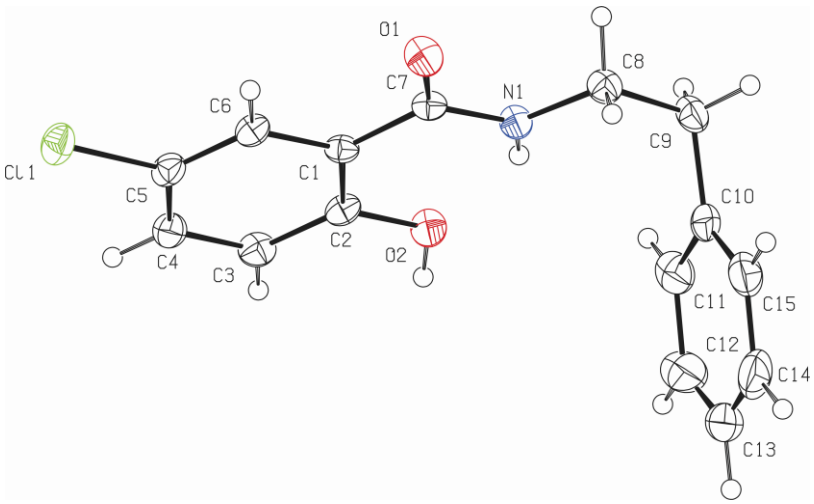


The factors that can generally contribute to a preference for one of the two arrangements of hydrogen bonds [32] include bond strength differences between intra- and intermolecular hydrogen bonds, steric demands (bulky substituents may enforce certain arrangement), cooperativity resulting from formation of the hydrogen-bonded chains or networks and competition for a limited number of proton donor and acceptor sites. However for *N*-substituted 2-hydroxybenzamides there is no obvious reason to expect that the formation of an internal NH ··O(H) bond would be favored over the formation of an internal C=O ··HO bond for the above-mentioned reasons.

The ability of an amide to act as a proton acceptor (C=O group is the site of protonation in amides) can be illustrated by the protonation acidity constants for structurally similar *N*-benzylbenzamide ($pK_a(BH^+) = -1.83$ in water [44]) and for related *N*-(4-methylphenyl)benzamide ($pK_a(BH^+) = -2.28$ in

water [45]). From the negligible difference in these two values it is clear that the acceptor ability of the amide carbonyl group towards protons is almost the same. The difference is much less than one log-unit *i.e.* less then one order of magnitude. On the other hand, amides behave as very weak *N*-acids and their dissociation constants were measured mostly in non-aqueous polar aprotic solvents. For example, in DMSO the following values can be found in the literature for *N*-phenylbenzamide (pK_a = 18.77) [46] and for structurally similar benzamide (pK_a = 23.35) [47]. Further substitution of benzamide nitrogen by an alkyl group (*e.g* benzyl) must cause an even higher difference in pK_a values, which is approximately 5 log-units *i.e.* around five orders of magnitude. From these values it is clear that *N*-aryl and *N*-alkyl substituted 2-hydroxybenzamides strongly differ in their acidity of the amide hydrogen from which it can be concluded that the hydrogen bond donor ability is much poorer for *N*-benzyl than for *N*-phenylsalicylamides. On the other hand the intrinsic hydrogen bond donor ability of the phenolic OH group measured by its pK_a value (*N*-phenylsalicylamide pK_a = 9.92 in water [48] and *N*-methylsalicylamide pK_a = 8.03 in water [49]) changes only by less than 2 log units (according to the literature [48]). In conclusion, in the molecule **2a** the amide group behaves as much a stronger proton donor than in **2b** and provides its hydrogen into a relatively strong hydrogen bond in which oxygen of the OH group acts as a hydrogen bond acceptor. In the molecule **2b** such a proton donor ability of the amide group is weaker (*ca.* 10^5-times less) and the proton donor ability of the OH group increases approximately 100-times at the same time. This gives rise to the formation of a new type of hydrogen bond with the amide carbonyl group acting as a hydrogen bond acceptor.

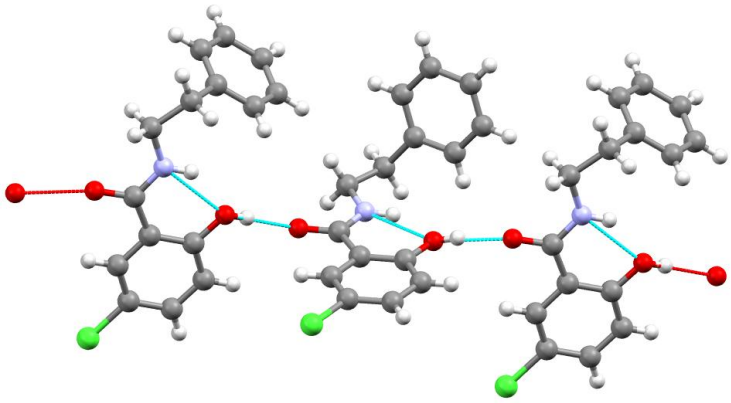
Figure 6. The ORTEP view of **2c** at 40% probability level.



According to above-mentioned explanation the molecule of **2c** should form the same hydrogen bond pattern like in **2b**. Available literature [50,51] describing crystal structures of *N*-substituted salicylamides containing ethylene linker also supports this idea. In fact for **2c** we observed intramolecular NH ··O(H) bonds between the amide and hydroxy groups (Figure 6) with perpendicularly oriented molecules thus forming an infinite chain as in the case of **2a** (Figure 7). This unexpected result would be caused by the solvent used for crystal growth. It is known from the literature [52] that the solvent can critically influence the formation of various polymorphic forms. We used relatively low polar chlorobenzene and got "open-ring" β-forms exclusively. Therefore we tried to crystallize the product **2c** from polar solvents (ethanol, ethylacetate) but we did not obtain any suitable

single crystal for further X-ray study. To the best of our knowledge this is the first case where this type of intramolecular hydrogen bond NH ··O(H) has been observed in the *N*-alkyl salicylamides which is normally characteristic for *N*-aryl salicylamides.

Figure 7. Packing pattern showing intermolecular H-bonding interactions found in the structure of **2c**.



3. Experimental Section

3.1. General

All reagents and solvents were purchased from commercial sources (5-chlorosalicylic acid (98%), 4-chloroaniline, benzylamine (ReagentPlus 99%), phenethylamine (99%) were purchased from Sigma-Aldrich, Phosphorus trichloride (99%) was purchased from Acros Organics, Chlorobenzene p.a. was obtained from Lach-Ner CZ). Commercial grade reagents were used without further purification. All the melting points were determined on a Melting Point B-545 apparatus (Büchi, Germany) and are uncorrected. The NMR spectra were measured in DMSO-d_6 solutions at ambient temperature on a Bruker Avance III 400 MHz spectrometer (Karlsruhe, Bruker, Germany, 400 MHz for ^{1}H, 100 MHz for ^{13}C). The X-ray data were obtained at 150K using Oxford Cryostream low-temperature device on a Nonius KappaCCD diffractometer with MoKα radiation (λ = 0.71073 Å), a graphite monochromator, and the φ and χ scan mode.

3.2. Synthesis

Phosphorus trichloride (30 mmol) was slowly added to a solution or suspension of 5-chloro salicylic acid (60 mmol) and corresponding amine **1a-c** (60 mmol) in chlorobenzene (250 mL). The reaction mixture was then heated under reflux in microwave reactor for 20 minutes under constant power (400 W). The hot reaction mixture was then transferred to the Erlenmeyer flask and slowly cooled down to ambient temperature. The solid was collected by filtration and recrystallized from absolute ethanol to give white crystals **2a-c**.

*3.3. Characterization of the Compounds **2a-c***

All the compounds were characterized using ^{1}H and ^{13}C NMR, as well as melting point of crystallized products. The purity was checked by CHN analyses. We also wanted to compare all data

with literature sources. Nevertheless, for the compound 5-chloro-*N*-(4-chlorophenyl)-2-hydroxybenzamide **2a** no found NMR characterization was found in the primary literature [53,54], therefore we show the ^{1}H and ^{13}C NMR interpretation as well as melting point and elemental analysis below. The analyses of the compound *N*-benzyl-5-chloro-2-hydroxybenzamide **2b** were in good agreement with literature source [55], for this compound we show only the data for elemental analyses, yield and melting point. The characterization of the third investigated molecule (5-chloro-2-hydroxy-*N*-phenethylbenzamide **2c**) was not also clearly shown in the literature [56], this was the reason to show results of the analyses as in the case **2a**.

5-Chloro-N-(4-chlorophenyl)-2-hydroxybenzamide **2a**: White crystals. Yield 82%, m.p. 227–229.3 °C (229–231 °C [39]). Anal. Calc. for $C_{13}H_9Cl_2NO_2$ (282.12): 55.34% C, 3.22% H, 4.96% N; found 55.42% C, 3.32% H, 5.01% N. ^{1}H NMR (DMSO-*d*6): δ = 11.73 (1H, bs, O*H*), 10.48 (1H, s, N*H*), 7.91 (1H, d, *J* = 2.7 Hz, H6), 7.74 (2H, m, AA', BB', overlapped, H2', H6'), 7.45 (1H, dd, overlapped, *J* = 8.7 Hz, *J* = 2.7 Hz, H4), 7.42 (2H, m, AA', BB', overlapped, H3', H5'), 7.01 (1H, d, *J* = 8.7 Hz, H3). ^{13}C NMR (DMSO-*d*6): δ = 164.9, 156.6, 137.0, 133.0, 128.6, 128.4, 127.9, 122.7, 122.2, 119.7, 119.0.

N-Benzyl-5-chloro-2-hydroxybenzamide 2b: White crystals. Yield 58%, m.p. 227–229.3 °C (229–231 °C [41]). Anal. Calc. for $C_{14}H_{12}ClNO_2$ (261.70): 64.25% C, 4.62% H, 5.35% N; found 64.26% C, 4.68% H, 5.38% N.

5-Chloro-2-hydroxy-N-phenethylbenzamide **2c**: White crystals. Yield 50%, m.p. 122–124 °C, ^{1}H NMR (DMSO-*d*6): δ = 12.59 (1H, bs, O*H*), 8.97 (1H, t, *J* = 5.4 Hz, N*H*), 7.93 (1H, d, *J* = 2.6 Hz, H6), 7.41 (1H, dd, *J* = 8.8 Hz, *J* = 2.2 Hz, H4), 7.32–7.19 (5H, m, H2', H3', H4', H5', H6'), 6.94 (1H, d, *J* = 9.16 Hz, H3) 3.54 (2H, q, *J* = 6.9 Hz, *J* = 6.5 Hz, CH_2), 2.87 (2H, t, *J* = 7.4 Hz, CH_2). ^{13}C-NMR (DMSO-*d*6): δ = 167.3, 158.5, 139.2. 133.2, 128.7, 128.4, 127.3, 126.2, 122.3, 119.3, 116.9, 40.7, 34.7.

3.4. Crystals Growth

Suitable crystals of the investigated compounds were obtained using the following procedure. The reaction mixture was cooled down after MW irradiation, and the precipitated products were collected by filtration. These crystals of crude **2a**-**2c** were dissolved in hot chlorobenzene at 100 °C. The mixture was slowly cooled down to 4 °C with a gradient 0.25 °C per minute. Crystal formed during this procedure were suitable for the X-ray measurement.

3.5. X-ray Data Collection and Structure Refinement

The X-ray data for the colorless crystals of 5-chloro-2-hydroxy-*N*-(4-chlorophenyl)benzamide (**2a**), 5-chloro-2-hydroxy-*N*-benzylbenzamide (**2b**) and 5-chloro-2-hydroxy-*N*-phenethylbenzamide (**2c**) were obtained at 150 K using a Oxford Cryostream low-temperature device on a Nonius KappaCCD diffractometer with MoKα radiation (λ = 0.71073 Å), a graphite monochromator, and the ϕ and χ scan mode. Data reductions were performed with DENZO-SMN [57]. The absorption was corrected by integration methods [58]. Structures were solved by direct methods (Sir92) [59] and refined by full

matrix least-square based on *F2* (SHELXL97) [60]. Hydrogen atoms were mostly localized on a difference Fourier map, however to ensure uniformity of the treatment of the crystal, all hydrogen atoms were recalculated into idealized positions (riding model) and assigned temperature factors $H_{iso}(H) = 1.2\ U_{eq}$(pivot atom) or of 1.5 U_{eq} for the methyl moiety with C–H = 0.97, and 0.93 Å for methylene and hydrogen atoms in aromatic rings moiety, respectively, O–H = 0.82 Å and N–H being 0.86 Å.

Crystallographic data for structural analysis were deposited with the Cambridge Crystallographic Data Centre. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EY, UK (Fax: +44-1223-336033; E-Mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

Crystallographic data for **2a** (5-chloro-2-hydroxy-*N*-phenylbenzamide): $C_{13}H_9Cl_2NO_2$, M = 282.11, monoclinic, $P2_1/c$, a = 19.9070(11), b = 4.7110(3), c = 12.6911(12) Å, β = 90.274(6) °, Z = 4, V = 1190.18(15) Å^3, D_c = 1.574 g.cm^{-3}, μ = 0.536 mm^{-1}, T_{min}/T_{max} = 0.954/0.978; $-25 \le h \le 22$, $-5 \le k \le 6$, $-14 \le l \le 16$; 7442 reflections measured (θ_{max} = 27.4 °), 2658 independent (R_{int} = 0.0464), 1995 with $I > 2\sigma(I)$, 163 parameters, S = 1.130, *R1*(obs. data) = 0.0440, *wR2*(all data) = 0.0830; max., min. residual electron density = 0.268, −0.351 eÅ^{-3}. CCDC Deposition number 859500.

Crystallographic data for **2b** (5-chloro-2-hydroxy-*N*-benzylbenzamide): $C_{14}H_{12}ClNO_2$, M = 261.70, monoclinic, $C2/c$, a = 26.9695(7), b = 6.6290(2), c = 16.0911(3) Å, β = 123.839(11) °, Z = 8, V = 2389.5(3) Å^3, D_c = 1.455 g cm^{-3}, μ = 0.312 mm^{-1}, T_{min}/T_{max} = 0.943/0.976; $-34 \le h \le 30$, $-7 \le k \le 8$, $-18 \le l \le 20$; 8389 reflections measured (θ_{max} = 27.5 °), 2708 independent (R_{int} = 0.0384), 2104 with $I > 2\sigma(I)$, 163 parameters, S = 1.100, *R1*(obs. data) = 0.0398, *wR2*(all data) = 0.0842; max., min. residual electron density = 0.309, −0.332 eÅ^{-3}. CCDC Deposition number: 859498.

Crystallographic data for **2c** (5-chloro-2-hydroxy-*N*-phenethylbenzamide): $C_{15}H_{14}ClNO_2$, M = 275.72, monoclinic, Pc, a = 12.4710(7), b = 4.7470(3), c = 12.8389(8) Å, β = 118.548(5) °, Z = 2, V = 667.65(8) Å^3, D_c = 1.372 g.cm^{-3}, μ = 0.283 mm^{-1}, T_{min}/T_{max} = 0.945/0.961; $-14 \le h \le 16$, $-6 \le k \le 5$, $-16 \le l \le 14$; 4418 reflections measured (θ_{max} = 27.49 °), 2376 independent (R_{int} = 0.0369), 2207 with $I > 2\sigma(I)$, 172 parameters, S = 1.105, *R1*(obs. data) = 0.0371, *wR2*(all data) = 0.0886; max., min. residual electron density = 0.195, –0.239 eÅ^{-3}. CCDC Deposition number: 859499.

4. Conclusions

The crystal structure of three 5-chloro substituted salicylamide derivatives were determined and registered in the Cambridge Crystallographic Data Centre. Two different types of hydrogen bonds were observed in the investigated structures. In 5-chloro-2-hydroxy-*N*-(4-chlorophenyl)benzamide (**2a**) and 5-chloro-2-hydroxy-*N*-phenethylbenzamide (**2c**) intramolecular NH ··O bond between the amide and hydroxy groups were observed. The molecules had an intermolecular contact between the hydroxy group and the C=O group thus forming a linear chain in the solid state. For the 5-chloro-2-hydroxy-*N*-benzylbenzamide (**2b**) an intramolecular bridge between the hydroxy and carbonyl group OH ··O, and another intermolecular NH ··O connection between the amide and hydroxy group were observed. The linear solid-state chain of (**2b**) was formed differently than in the case of compounds **2a** and **2c**.

Acknowledgments

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