

ON THE RELATIONSHIP BETWEEN THE STRUCTURE AND ANTIMYCOBACTERIAL ACTIVITY OF SUBSTITUTED *N*-BENZYL SALICYLAMIDES

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Received December 2, 2002

Accepted April 17, 2003

This paper is dedicated to Professor Václav Horák on the occasion of his 80th birthday.

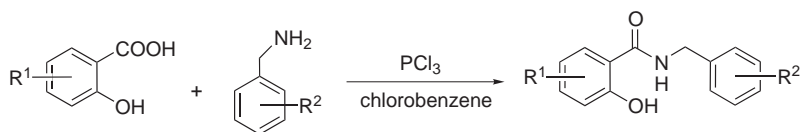
Sixty-six *N*-benzylsalicylamides substituted in the acyl moiety in positions 3, 4 or 5 and in position 4 on the benzylic aromatic ring were synthesized. The compounds were tested for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis*, *Mycobacterium kansasii* and *Mycobacterium avium*. To evaluate structure–antimycobacterial activity relationships (QSARs), approaches based on the Free–Wilson as well as a combination of the Free–Wilson and Hansch methods were employed (substituent constants were used to describe the influence of the benzyl substituents, indicator parameters were used for the substituents on the acyl moiety). The use of the Hammett constants for benzyl substituents was not important for QSAR equations. The quadratic representation of lipophilicity parameters (π^2) was significant only in QSAR equations of antimycobacterial activity against *M. avium*.

Keywords: Tuberculostatic; Antituberculotics; Salicylamides; QSAR; Substituent effects; Structure–activity relationships; Antimicrobial activity; Free–Wilson method.

Search for new antimycobacterial compounds is one of the most challenging tasks of current medicinal chemistry. In particular, the study of antimycobacterial properties of salicylanilides^{1,2} is of great interest, as salicylanilides are inhibitors of bacterial two-component systems^{3,4}, which can be also important in mycobacteria. The goal of this paper was to study the antimycobacterial activity of *N*-benzylsalicylamides. Given the similarity in structure, we assumed that *N*-benzylsalicylamides could be a new group of potential antituberculotics acting by inhibition of two-component systems

in Mycobacteria as well. The antimycobacterial activity of other compounds isosteric to salicylanilides has been described recently⁵.

N-Benzylsalicylamides were prepared by treatment of substituted salicylic acids with benzylamines (Scheme 1). The compounds were characterized by NMR and IR spectroscopy. In the IR spectra, the carbonyl vibration $\nu(\text{C}=\text{O})$ was observed in the region 1626–1651 cm^{-1} .



1–6	R ¹	1–6	R ¹		R ²
a	H	g	4-OCH ₃	1	H
b	5-Br	h	5-NO ₂	2	4-Cl
c	5-Cl	i	4-Cl	3	4-CH ₃
d	3,5-Cl ₂	j	3-OCH ₃	4	4-F
e	5-CH ₃	k	5-OCH ₃	5	3,4-Cl ₂
f	3,5-Br ₂			6	4-OCH ₃

SCHEME 1

The antimycobacterial activity of the synthesized *N*-benzylsalicylamides is given in Table I. Unlike isoniazid, the most active compounds exhibited consistent activity against all mycobacterial strains of the testing panel. Their broad spectrum of activity can be considered as an advantage. Thus, we have identified a new group of potential antituberculotics – *N*-benzylsalicylamides.

EXPERIMENTAL

Synthesis

The melting points were determined on a Kofler apparatus. The samples for analysis and antimycobacterial tests were dried over P₂O₅ at 61 °C and 66 Pa for 24 h. Elemental analyses (C, H, N) were performed on a CHNS-O CE elemental analyzer (Fisions EA 1110, Milan) and were within ±0.4% of the theoretical values. The IR spectra were measured in KBr pellets on a Nicolet Impact 400 apparatus; the wavenumbers are given in cm^{-1} . TLC was performed on silica gel plates precoated with a fluorescent indicator Silufol UV 254 + 366 (Kavalier Votice, Czech Republic), cyclohexane–acetone (3:1) was used as the mobile phase. The ¹H NMR and ¹³C NMR spectra of new compounds were recorded in CDCl₃ or DMSO-*d*₆ solutions at ambient temperature on a Varian Mercury-Vx BB 300 spectrometer operating at 300 MHz for ¹H NMR and 75 MHz for ¹³C NMR. Chemical shifts were recorded as δ values in ppm and

TABLE I
Minimum inhibitory concentrations of *N*-benzylsalicylamides substituted in positions 3, 4 and 5

Com- pounds	MIC, $\mu\text{mol/l}$ incubation 14 d/21 d					
	R ¹	R ²	<i>M. tuberculosis</i> <i>My 331/88</i>	<i>M. avium</i> <i>My 330/88</i>	<i>M. kansasii</i> <i>My 235/80</i>	<i>M. kansasii</i> <i>6509/96</i>
1a	H	H	<i>a/a</i>	125/125	<i>a/a</i>	<i>a/a</i>
1b	5-Br	H	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>
1c	5-Cl	H	62/ <i>a</i>	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>
1d	3,5-Cl ₂	H	32/62	125/125	125/125	125/125
1e	5-CH ₃	H	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>
1f	3,5-Br ₂	H	32/32	125/125	125/125	125/125
1g	4-CH ₃ O	H	125/ <i>a</i>	125/ <i>a</i>	<i>a/a</i>	<i>a/a</i>
1h	5-NO ₂	H	125/125	<i>a/a</i>	250/250	250/500
1i	4-Cl	H	62/62	62/62	125/125	125/ <i>a</i>
1j	3-CH ₃ O	H	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>
1k	5-CH ₃ O	H	250/250	125/250	32/62	125/250
2a	H	4-Cl	32/62	16/32	62/ <i>a</i>	62/ <i>a</i>
2b	5-Br	4-Cl	32/32	16/16	32/32	32/32
2c	5-Cl	4-Cl	32/32	16/16	32/32	32/32
2d	3,5-Cl ₂	4-Cl	32/62	62/62	62/62	62/62
2e	5-CH ₃	4-Cl	32/32	16/32	62/ <i>a</i>	62/62
2f	3,5-Br ₂	4-Cl	32/32	62/62	62/62	62/62
2g	4-CH ₃ O	4-Cl	32/32	32/32	62/ <i>a</i>	62/62
2h	5-NO ₂	4-Cl	32/32	125/250	125/125	125/250
2i	4-Cl	4-Cl	32/32	32/32	32/32	32/32
2j	3-CH ₃ O	4-Cl	62/125	62/125	125/500	62/125
2k	5-CH ₃ O	4-Cl	<i>a/a</i>	32/ <i>a</i>	62/ <i>a</i>	<i>a/a</i>
3a	H	4-CH ₃	125/125	32/62	125/ <i>a</i>	125/ <i>a</i>
3b	5-Br	4-CH ₃	<i>a/a</i>	32/32	62/62	62/ <i>a</i>
3c	5-Cl	4-CH ₃	32/62	32/32	62/62	62/62
3d	3,5-Cl ₂	4-CH ₃	62/62	62/62	62/62	125/125
3e	5-CH ₃	4-CH ₃	62/ <i>a</i>	32/62	62/ <i>a</i>	62/ <i>a</i>
3f	3,5-Br ₂	4-CH ₃	62/62	62/62	62/62	62/62
3g	4-CH ₃ O	4-CH ₃	125/ <i>a</i>	62/62	<i>a/a</i>	<i>a/a</i>
3h	5-NO ₂	4-CH ₃	32/32	500/500	250/250	125/250
3i	4-Cl	4-CH ₃	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>
3j	3-CH ₃ O	4-CH ₃	125/125	125/250	125/250	250/250
3k	5-CH ₃ O	4-CH ₃	125/ <i>a</i>	62/ <i>a</i>	62/125	125/125
4a	H	4-F	250/250	125/125	125/250	125/125

TABLE I
(Continued)

Com- pounds	MIC, $\mu\text{mol/l}$ incubation 14 d/21 d					
	R ¹	R ²	<i>M. tuberculosis</i> <i>My 331/88</i>	<i>M. avium</i> <i>My 330/88</i>	<i>M. kansasii</i> <i>My 235/80</i>	<i>M. kansasii</i> <i>6509/96</i>
4b	5-Br	4-F	32/62	62/62	<i>a/a</i>	62/62
4c	5-Cl	4-F	62/62	32/62	62/ <i>a</i>	62/62
4d	3,5-Cl ₂	4-F	32/62	125/125	125/125	125/125
4e	5-CH ₃	4-F	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>
4f	3,5-Br ₂	4-F	32/32	62/62	62/62	62/62
4g	4-CH ₃ O	4-F	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>
4h	5-NO ₂	4-F	62/62	1000/1000	250/500	250/250
4i	4-Cl	4-F	32/62	62/62	62/62	62/62
4j	3-CH ₃ O	4-F	250/250	250/ <i>a</i>	250/250	250/250
4k	5-CH ₃ O	4-F	250/ <i>a</i>	62/125	125/125	125/125
5a	H	3,4-Cl ₂	32/62	32/62	62/125	32/62
5b	5-Br	3,4-Cl ₂	16/32	16/32	32/32	32/32
5c	5-Cl	3,4-Cl ₂	16/32	16/32	32/62	32/32
5d	3,5-Cl ₂	3,4-Cl ₂	32/62	62/62	62/62	62/62
5e	5-CH ₃	3,4-Cl ₂	32/ <i>a</i>	32/ <i>a</i>	<i>a/a</i>	62/ <i>a</i>
5f	3,5-Br ₂	3,4-Cl ₂	32/32	62/62	32/62	32/62
5g	4-CH ₃ O	3,4-Cl ₂	32/32	62/62	62/62	62/62
5h	5-NO ₂	3,4-Cl ₂	16/16	125/125	62/62	62/125
5i	4-Cl	3,4-Cl ₂	16/32	32/32	62/62	32/32
5j	3-CH ₃ O	3,4-Cl ₂	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>	<i>a/a</i>
5k	5-CH ₃ O	3-Cl	125/250	125/250	62/62	125/250
6a	H	4-CH ₃ O	125/125	125/250	125/125	125/250
6b	5-Br	4-CH ₃ O	32/62	62/62	62/62	125/125
6c	5-Cl	4-CH ₃ O	62/62	62/62	<i>a/125</i>	125/ <i>a</i>
6d	3,5-Cl ₂	4-CH ₃ O	62/62	250/250	125/125	125/125
6e	5-CH ₃	4-CH ₃ O	125/ <i>a</i>	125/125	<i>a/a</i>	<i>a/a</i>
6f	3,5-Br ₂	4-CH ₃ O	62/62	125/125	32/62	32/62
6g	4-CH ₃ O	4-CH ₃ O	62/62	250/250	125/250	125/125
6h	5-NO ₂	4-CH ₃ O	8/16	1000/1000	125/250	125/250
6i	4-Cl	4-CH ₃ O	32/32	62/62	62/125	62/125
6j	3-CH ₃ O	4-CH ₃ O	125/250	250/500	250/500	250/500
6k	5-CH ₃ O	4-CH ₃ O	125/250	62/125	125/125	62/125
INH			0.5/1	250/250	250/250	4/4

a: MIC values could not be determined due to the low solubility. The values of compounds **1a**, **2a**, **3a**, **4a**, **5a** and **6a** were taken from the ref.⁶

being indirectly referenced to tetramethylsilane *via* the solvent signal (2.49 for ^1H or 39.7 for ^{13}C). Coupling constants (J) are given in Hz.

Preparation of *N*-Benzylsalicylamides 1–6. General Procedure

A suspension of a substituted salicylic acid (0.02 mol) and substituted benzylamine (0.02 mol) in chlorobenzene (100 ml) was heated under reflux in the presence of PCl_3 (0.01 mol) for 3 h. The reaction mixture was filtered while hot, and the solvents were evaporated. The product was crystallized from ethanol–water (yields in the range 75–95%). The synthesis and physical properties of the compounds **1a**, **2a**, **3a**, **4a**, **5a** and **6a** were described in our previous paper⁶.

5-Bromo-*N*-benzylsalicylamide (1b). White crystals. Yield 65%, m.p. 152–154 °C (ref.⁷ 154–156 °C). IR: $\nu(\text{C}=\text{O})$ 1640. ^1H NMR ($\text{DMSO}-d_6$): 12.60 s, 1 H (OH); 9.40 t, 1 H, $J = 6.00$ (NH); 8.12 d, 1 H, $J(4,6) = 2.70$ (H6); 7.54 dd, 1 H, $J(3,4) = 9.00$, $J(4,6) = 2.70$ (H4); 7.35–7.20 m, 5 H (H2', H3', H4', H5', H6'); 6.95 d, 1 H, $J(3,4) = 9.00$ (H3); 4.51 d, 2 H, $J = 6.00$ (CH_2). ^{13}C NMR ($\text{DMSO}-d_6$): 167.7, 159.3, 138.9, 136.3, 130.4, 128.6, 127.6, 127.2, 120.0, 117.5, 110.0, 42.8.

***N*-Benzyl-5-chlorosalicylamide (1c)**. White crystals. Yield 63%, m.p. 144–145 °C (ref.⁷ 145–146 °C). IR: $\nu(\text{C}=\text{O})$ 1643. ^1H NMR ($\text{DMSO}-d_6$): 12.52 s, 1 H (OH); 9.39 t, 1 H, $J = 5.70$ (NH); 7.98 d, 1 H, $J(4,6) = 2.40$ (H6); 7.54 dd, 1 H, $J(3,4) = 9.00$, $J(4,6) = 2.40$ (H4); 7.38–7.22 m, 5 H (H2', H3', H4', H5', H6'); 6.95 d, 1 H, $J(3,4) = 9.00$ (H3); 4.50 d, 2 H, $J = 5.70$ (CH_2). ^{13}C NMR ($\text{DMSO}-d_6$): 167.7, 158.8, 138.9, 133.5, 128.6, 127.6, 127.5, 127.2, 122.6, 119.5, 117.0, 42.7.

***N*-Benzyl-3,5-dichlorosalicylamide (1d)**. White crystals. Yield 50%, m.p. 119–120 °C. IR: $\nu(\text{C}=\text{O})$ 1642. For $\text{C}_{14}\text{H}_{11}\text{Cl}_2\text{NO}_2$ (296.2) calculated: 56.78% C, 3.74% H, 4.73% N; found: 56.80% C, 3.76% H, 4.70% N. ^1H NMR ($\text{DMSO}-d_6$): 9.70 t, 1 H, $J = 6.00$ (NH); 8.05 d, 1 H, $J(4,6) = 2.10$ (H6); 7.75 d, 1 H, $J(4,6) = 2.10$ (H4); 7.38–7.22 m, 5 H (H2', H3', H4', H5', H6'); 4.50 d, 2 H, $J = 6.00$ (CH_2). ^{13}C NMR ($\text{DMSO}-d_6$): 168.4, 156.0, 138.3, 133.3, 128.6, 127.6, 127.3, 125.8, 122.6, 122.2, 116.5, 42.9.

***N*-Benzyl-5-methylsalicylamide (1e)**. White crystals. Yield 91%, m.p. 134–135.5 °C. IR: $\nu(\text{C}=\text{O})$ 1645. For $\text{C}_{15}\text{H}_{15}\text{NO}_2$ (241.3) calculated: 74.67% C, 6.27% H, 5.81% N; found: 74.54% C, 6.35% H, 5.69% N. ^1H NMR (CDCl_3): 12.14 s, 1 H (OH); 7.40–7.29 m, 5 H (H2', H3', H4', H5', H6'); 7.22–7.17 m, 2 H (H4, H6); 6.89 d, 1 H, $J(3,4) = 8.40$ (H3); 6.76 bs, 1 H (NH); 4.61 d, 2 H, $J = 5.70$ (CH_2); 2.25 s, 3 H (CH_3). ^{13}C NMR (CDCl_3): 169.8, 159.2, 137.4, 135.2, 128.8, 127.8, 127.8, 127.7, 125.4, 118.2, 113.6, 43.5, 20.4.

***N*-Benzyl-3,5-dibromosalicylamide (1f)**. White crystals. Yield 73%, m.p. 126–126 °C. IR: $\nu(\text{C}=\text{O})$ 1641. For $\text{C}_{14}\text{H}_{11}\text{Br}_2\text{NO}_2$ (385.1) calculated: 43.67% C, 2.88% H, 3.64% N; found: 43.49% C, 2.91% H, 3.51% N. ^1H NMR ($\text{DMSO}-d_6$): 9.72 t, 1 H, $J = 5.70$ (NH); 8.20 d, 1 H, $J(4,6) = 2.10$ (H6); 7.96 d, 1 H, $J(4,6) = 2.10$ (H4); 7.37–7.23 m, 5 H (H2', H3', H4', H5', H6'); 4.51 d, 2 H, $J = 5.70$ (CH_2). ^{13}C NMR ($\text{DMSO}-d_6$): 168.3, 157.4, 138.7, 138.3, 129.2, 128.6, 127.7, 127.3, 116.8, 112.4, 109.8, 42.9.

***N*-Benzyl-4-methoxysalicylamide (1g)**. White crystals. Yield 69%, m.p. 105–110 °C. IR: $\nu(\text{C}=\text{O})$ 1641. For $\text{C}_{15}\text{H}_{15}\text{NO}_3$ (257.3) calculated: 70.02% C, 5.88% H, 5.44% N; found: 70.13% C, 5.89% H, 5.37% N. ^1H NMR (CDCl_3): 7.39–7.29 m, 5 H (H2', H3', H4', H5', H6'); 7.25 d, 1 H, $J(4,6) = 9.00$ (H6); 6.48 bs overlapped, 1 H (NH); 6.47 d overlapped, 1 H, $J(3,5) = 2.40$ (H3); 7.54 dd, 1 H, $J(5,6) = 9.00$, $J(3,5) = 2.40$ (H5); 4.60 d, 2 H, $J = 5.70$ (CH_2); 3.79 s,

3 H (OCH₃). ¹³C NMR (CDCl₃): 169.7, 164.4, 163.8, 137.6, 128.8, 127.8, 127.7, 126.6, 107.0, 106.9, 101.5, 55.4, 43.5.

N-Benzyl-5-nitrosalicylamide (**1h**). Yellow crystals. Yield 62%, m.p. 152–154 °C (ref.⁸ 161.5–162.5 °C). IR: ν(C=O) 1649. For C₁₄H₁₂N₂O₄ (272.3) calculated: 61.76% C, 4.44% H, 10.29% N; found: 61.78% C, 4.53% H, 10.34% N. ¹H NMR (DMSO-*d*₆): 9.66 t, 1 H, *J* = 6.00 (NH); 8.89 d, 1 H, *J*(4,6) = 3.00 (H6); 8.25 dd, 1 H, *J*(3,4) = 9.30, *J*(4,6) = 3.00 (H4); 7.37–7.23 m, 5 H (H2', H3', H4', H5', H6'); 7.10 d, 1 H, *J*(3,4) = 9.30 (H3); 4.53 d, 2 H, *J* = 6.00 (CH₂). ¹³C NMR (DMSO-*d*₆): 167.0, 165.3, 139.4, 138.7, 129.0, 128.6, 127.7, 127.3, 125.1, 118.6, 116.1, 42.9.

N-Benzyl-4-chlorosalicylamide (**1i**). White crystals. Yield 64%, m.p. 129–132 °C (ref.⁹ 124–127 °C). IR: ν(C=O) 1636. For C₁₄H₁₂ClNO₂ (261.7) calculated: 64.25% C, 4.62% H, 5.35% N; found: 64.12% C, 4.69% H, 5.28% N. ¹H NMR (CDCl₃): 12.53 s, 1 H (OH); 7.40–7.26 m, 6 H (H6, H2', H3', H4', H5', H6'); 6.99 d, 1 H, *J*(3,5) = 3.00 (H3); 6.80 dd, 1 H, *J*(5,6) = 8.40, *J*(3,5) = 3.00 (H5); 6.62 bs, 1 H (NH); 4.61 d, 2 H, *J* = 5.40 (CH₂). ¹³C NMR (CDCl₃): 169.1, 162.3, 139.8, 137.0, 128.9, 127.9, 127.8, 126.3, 119.1, 118.6, 112.6, 43.7.

N-Benzyl-3-methoxysalicylamide (**1j**). White crystals. Yield 33%, m.p. 127–129 °C (ref.¹⁰ 134 °C). IR: ν(C=O) 1641. For C₁₅H₁₅NO₃ (257.3) calculated: 70.02% C, 5.88% H, 5.44% N; found: 69.91% C, 5.69% H, 5.32% N. ¹H NMR (CDCl₃): 11.85 bs, 1 H (OH); 7.34–7.27 m, 5 H (H2', H3', H4', H5', H6'); 7.18 bs overlapped, 1 H (NH); 7.12 dd overlapped, 1 H, *J*(5,6) = 8.05, *J*(4,6) = 1.20 (H6); 6.95 dd, 1 H, *J*(4,5) = 8.05, *J*(4,6) = 1.20 (H4); 6.80 t, 1 H, *J* = 8.05 (H5); 4.60 d, 2 H, *J* = 5.70 (CH₂); 3.85 s, 3 H (OCH₃). ¹³C NMR (CDCl₃): 169.2, 150.7, 148.7, 137.5, 128.7, 127.7, 127.6, 118.3, 117.8, 114.8, 114.6, 56.0, 43.5.

N-Benzyl-5-methoxysalicylamide (**1k**). White crystals. Yield 18%, m.p. 94–97 °C. IR: ν(C=O) 1644. For C₁₅H₁₅NO₃ (257.3) calculated: 70.02% C, 5.88% H, 5.44% N; found: 70.21% C, 5.84% H, 5.41% N. ¹H NMR (CDCl₃): 11.77 s, 1 H (OH); 7.40–7.28 m, 5 H (H2', H3', H4', H5', H6'); 7.02 dd, 1 H, *J*(3,4) = 9.00, *J*(4,6) = 3.00 (H4); 6.93 d, 1 H, *J*(3,4) = 9.00 (H3); 6.83 d, 1 H, *J*(4,6) = 3.00 (H6); 6.64 bs, 1 H (NH); 4.62 d, 2 H, *J* = 5.70 (CH₂); 3.74 s, 3 H (OCH₃). ¹³C NMR (CDCl₃): 169.5, 155.5, 151.8, 137.4, 128.9, 127.9, 127.8, 121.0, 119.3, 113.9, 109.7, 56.0, 43.7.

5-Bromo-*N*-(4-chlorobenzyl)salicylamide (**2b**). White crystals. Yield 53%, m.p. 152–155 °C (ref.⁷ 158–159 °C). IR: ν(C=O) 1621. ¹H NMR (CDCl₃): 12.16 s, 1 H (OH); 7.48–7.44 m, 2 H (H4, H6); 7.35–7.23 m AA' BB', 4 H (H2', H3', H5', H6'); 6.88 d, 1 H, *J*(3,4) = 9.30 (H3); 6.62 bs, 1 H (NH); 4.57 d, 2 H, *J* = 5.70 (CH₂). ¹³C NMR (CDCl₃): 168.7, 160.5, 137.1, 135.5, 133.8, 129.3, 129.0, 127.9, 120.6, 115.5, 110.3, 43.1.

5-Chloro-*N*-(4-chlorobenzyl)salicylamide (**2c**). White crystals. Yield 58%, m.p. 154–155 °C (ref.⁷ 156–158 °C). IR: ν(C=O) 1621. ¹H NMR (CDCl₃): 12.14 s, 1 H (OH); 7.37–7.27 m, 6 H (H4, H6, H2', H3', H5', H6'); 6.94 d, 1 H, *J*(3,4) = 8.70 (H3); 6.57 bs, 1 H (NH); 4.59 d, 2 H, *J* = 5.70 (CH₂). ¹³C NMR (CDCl₃): 168.8, 160.1, 135.6, 134.3, 133.9, 129.3, 129.1, 124.9, 123.4, 120.2, 114.8, 43.1.

3,5-Dichloro-*N*-(4-chlorobenzyl)salicylamide (**2d**). White crystals. Yield 69%, m.p. 124–126 °C. IR: ν(C=O) 1647. For C₁₄H₁₀Cl₃NO₂ (330.6) calculated: 50.86% C, 3.05% H, 4.24% N; found: 50.67% C, 3.28% H, 4.18% N. ¹H NMR (DMSO-*d*₆): 9.70 t, 1 H, *J* = 5.70 (NH); 8.02 d, 1 H, *J*(4,6) = 2.40 (H6); 7.76 d, 1 H, *J*(4,6) = 2.40 (H4); 7.40–7.32 m, 4 H (H2', H3', H5', H6'); 4.48 d, 2 H, *J* = 5.70 (CH₂). ¹³C NMR (DMSO-*d*₆): 168.4, 156.0, 137.4, 133.4, 131.9, 129.6, 128.6, 125.9, 122.6, 122.3, 116.5, 42.3.

N-(4-Chlorobenzyl)-5-methylsalicylamide (**2e**). White crystals. Yield 37%, m.p. 110–114 °C. IR: ν(C=O) 1644. For C₁₅H₁₄ClNO₂ (275.5) calculated: 65.34% C, 5.12% H, 5.08% N; found:

65.57% C, 5.39% H, 5.08% N. ^1H NMR (CDCl_3): 12.02 s, 1 H (OH); 7.33–7.15 m, 6 H (H4, H6, H2', H3', H5', H6'); 6.88 d, 1 H, $J(3,4) = 8.10$ (H3); 6.72 bs, 1 H (NH); 4.57 d, 2 H, $J = 5.70$ (CH_2); 2.52 s, 3 H (CH_3). ^{13}C NMR (CDCl_3): 169.9, 159.3, 136.0, 135.4, 133.5, 129.1, 128.9, 127.9, 125.3, 118.3, 113.5, 42.8, 20.4.

3,5-Dibromo-*N*-(4-chlorobenzyl)salicylamide (2f). White crystals. Yield 68%, m.p. 138–140 °C (ref.¹¹ 139–142 °C). IR: $\nu(\text{C}=\text{O})$ 1641. ^1H NMR (CDCl_3): 7.78 d, 1 H, $J(4,6) = 2.40$ (H6); 7.47 d, 1 H, $J(4,6) = 2.40$ (H4); 7.34–7.31 m AA' BB', 2 H (H2', H6'); 7.29–7.24 m AA' BB', 2 H (H3', H5'); 6.69 bs, 1 H (NH); 4.59 d, 2 H, $J = 5.70$ (CH_2). ^{13}C NMR (CDCl_3): 168.0, 157.3, 139.6, 135.2, 134.0, 129.3, 129.1, 127.4, 116.1, 113.5, 110.1, 43.3.

***N*-(4-Chlorobenzyl)-4-methoxysalicylamide (2g)**. White crystals. Yield 58%, m.p. 115–117.5 °C. IR: $\nu(\text{C}=\text{O})$ 1641. For $\text{C}_{15}\text{H}_{14}\text{ClNO}_3$ (291.7) calculated: 61.76% C, 4.84% H, 4.80% N; found: 61.44% C, 4.82% H, 4.90% N. ^1H NMR (CDCl_3): 7.33–7.15 m, 5 H (H6, H2', H3', H5', H6'); 6.51 bs overlapped, 1 H (NH); 6.46 d overlapped, 1 H, $J(3,5) = 2.40$ (H3); 6.37 dd, 1 H, $J(5,6) = 9.00$, $J(3,5) = 2.40$ (H5); 4.56 d, 2 H, $J = 5.70$ (CH_2); 3.80 s, 3 H (OCH_3). ^{13}C NMR (CDCl_3): 169.8, 164.5, 163.8, 136.2, 133.5, 129.1, 128.9, 126.6, 107.1, 106.8, 101.5, 55.4, 42.8.

***N*-(4-Chlorobenzyl)-5-nitrosalicylamide (2h)**. Yellow crystals. Yield 62%, m.p. 212–214 °C. IR: $\nu(\text{C}=\text{O})$ 1648. For $\text{C}_{14}\text{H}_{11}\text{ClN}_2\text{O}_4$ (306.7) calculated: 54.83% C, 3.62% H, 9.13% N; found: 54.92% C, 3.72% H, 8.99% N. ^1H NMR ($\text{DMSO}-d_6$): 9.65 t, 1 H, $J = 5.70$ (NH); 8.86 d, 1 H, $J(4,6) = 2.70$ (H6); 8.24 dd, 1 H, $J(3,4) = 9.00$, $J(4,6) = 2.70$ (H4); 7.40–7.37 m, 4 H (H2', H3', H5', H6'); 7.10 d, 1 H, $J(3,4) = 9.00$ (H3); 4.52 d, 2 H, $J = 5.70$ (CH_2). ^{13}C NMR ($\text{DMSO}-d_6$): 167.0, 165.2, 139.4, 137.8, 131.8, 129.5, 129.0, 128.5, 125.2, 118.6, 116.2, 42.3.

4-Chloro-*N*-(4-chlorobenzyl)salicylamide (2i). White crystals. Yield 95%, m.p. 164–166 °C. IR: $\nu(\text{C}=\text{O})$ 1632. For $\text{C}_{14}\text{H}_{11}\text{Cl}_2\text{NO}_2$ (296.2) calculated: 56.78% C, 3.74% H, 4.73% N; found: 56.68% C, 4.01% H, 4.58% N. ^1H NMR ($\text{DMSO}-d_6$): 9.38 t, 1 H, $J = 6.00$ (NH); 7.90 d, 1 H, $J(5,6) = 8.10$ (H6); 7.33–7.15 m, 4 H (H2', H3', H5', H6'); 6.99 dd, 1 H, $J(5,6) = 8.10$, $J(3,5) = 1.80$ (H5); 6.95 d, 1 H, $J(3,5) = 1.80$ (H3); 4.48 d, 2 H, $J = 6.00$ (CH_2). ^{13}C NMR ($\text{DMSO}-d_6$): 168.1, 160.8, 138.1, 137.9, 131.7, 129.9, 129.4, 128.5, 119.2, 117.2, 114.8, 42.0.

***N*-(4-Chlorobenzyl)-3-methoxysalicylamide (2j)**. White crystals. Yield 48%, m.p. 127–129 °C. IR: $\nu(\text{C}=\text{O})$ 1638. For $\text{C}_{15}\text{H}_{14}\text{ClNO}_3$ (291.7) calculated: 61.76% C, 4.84% H, 4.80% N; found: 61.84% C, 4.75% H, 4.95% N. ^1H NMR (CDCl_3): 11.49 s, 1 H (OH); 7.28–7.19 m, 4 H (H2', H3', H5', H6'); 7.22 bs overlapped, 1 H (NH); 7.15 d, 1 H, $J(5,6) = 7.80$ (H6); 6.96 d, 1 H, $J(4,5) = 7.80$ (H4); 6.80–6.75 m, 1 H (H5); 4.56 d, 2 H, $J = 5.70$ (CH_2); 3.86 s, 3 H (OCH_3). ^{13}C NMR (CDCl_3): 169.1, 150.4, 148.6, 136.2, 133.3, 129.0, 128.8, 118.5, 118.0, 114.8, 114.6, 56.0, 42.9.

***N*-(4-Chlorobenzyl)-5-methoxysalicylamide (2k)**. White crystals. Yield 50%, m.p. 157.5–159 °C. IR: $\nu(\text{C}=\text{O})$ 1644. For $\text{C}_{15}\text{H}_{14}\text{ClNO}_3$ (291.7) calculated: 61.76% C, 4.84% H, 4.80% N; found: 61.63% C, 4.72% H, 4.79% N. ^1H NMR ($\text{DMSO}-d_6$): 11.96 s, 1 H (OH); 9.35 t, 1 H, $J = 6.30$ (NH); 7.44 d, 1 H, $J = 3.00$ (H6); 7.40–7.31 m, 4 H (H2', H3', H5', H6'); 7.25 dd, 1 H, $J(4,6) = 9.00$, $J(4,6) = 3.00$ (H4); 6.84 d, 1 H, $J(3,4) = 9.00$ (H3); 4.51 d, 2 H, $J = 6.30$ (CH_2); 3.72 s, 3 H (OCH_3). ^{13}C NMR ($\text{DMSO}-d_6$): 168.8, 154.2, 151.8, 138.3, 131.7, 129.4, 128.6, 121.3, 118.5, 115.1, 111.3, 55.9, 42.0.

5-Bromo-*N*-(4-methylbenzyl)salicylamide (3b). White crystals. Yield 63%, m.p. 157–160 °C. IR: $\nu(\text{C}=\text{O})$ 1622. For $\text{C}_{15}\text{H}_{14}\text{BrNO}_2$ (320.2) calculated: 56.27% C, 4.41% H, 4.37% N; found: 55.92% C, 4.33% H, 4.22% N. ^1H NMR ($\text{DMSO}-d_6$): 12.60 s, 1 H (OH); 9.35 t, 1 H, $J = 5.70$ (NH); 8.10 d, 1 H, $J(4,6) = 2.70$ (H6); 7.53 dd, 1 H, $J(3,4) = 8.70$, $J(4,6) = 2.70$ (H4); 7.22–7.10 m AA' BB', 4 H (H2', H3', H5', H6'); 6.88 d, 1 H, $J(3,4) = 8.70$ (H3); 4.45 d, 2 H, $J = 5.70$

(CH₂); 2.26 s, 3 H (CH₃). ¹³C NMR (DMSO-*d*₆): 167.6, 129.3, 136.3, 136.3, 135.8, 130.4, 129.1, 127.6, 120.0, 117.5, 110.0, 42.5, 20.9.

5-Chloro-*N*-(4-methylbenzyl)salicylamide (3c). White crystals. Yield 38%, m.p. 157–159 °C. IR: ν(C=O) 1622. For C₁₅H₁₄ClNO₂ (275.5) calculated: 65.34% C, 5.12% H, 5.08% N; found: 65.76% C, 5.13% H, 5.29% N. ¹H NMR (DMSO-*d*₆): 12.48 s, 1 H (OH); 9.35 t, 1 H, *J* = 5.70 (NH); 7.98 d, 1 H, *J*(4,6) = 2.70 (H6); 7.42 dd, 1 H, *J*(3,4) = 9.00, *J*(4,6) = 2.70 (H4); 7.22–7.11 m AA' BB', 4 H (H2', H3', H5', H6'); 6.88 d, 1 H, *J*(3,4) = 9.00 (H3); 4.45 d, 2 H, *J* = 5.70 (CH₂); 2.26 s, 3 H (CH₃). ¹³C NMR (DMSO-*d*₆): 167.6, 158.8, 136.3, 135.8, 133.5, 129.1, 127.6, 127.6, 122.6, 119.5, 116.9, 42.5, 20.9.

3,5-Dichloro-*N*-(4-methylbenzyl)salicylamide (3d). White crystals. Yield 57%, m.p. 110–112 °C. IR: ν(C=O) 1646. For C₁₅H₁₃Cl₂NO₂ (310.2) calculated: 58.08% C, 4.22% H, 4.52% N; found: 58.46% C, 4.03% H, 4.29% N. ¹H NMR (CDCl₃): 7.47 d, 1 H, *J*(4,6) = 2.40 (H6); 7.28 d, 1 H, *J*(4,6) = 2.40 (H4); 7.25–7.15 m AA' BB', 4 H (H2', H3', H5', H6'); 6.69 bs, 1 H (NH); 4.56 d, 2 H, *J* = 5.40 (CH₂); 2.35 s, 3 H (CH₃). ¹³C NMR (CDCl₃): 168.0, 156.0, 137.9, 133.8, 133.5, 129.6, 128.0, 124.0, 123.8, 123.0, 115.8, 43.82, 21.1.

5-Methyl-*N*-(4-methylbenzyl)salicylamide (3e). White crystals. Yield 68%, m.p. 103–105 °C. IR: ν(C=O) 1641. For C₁₆H₁₇NO₂ (275.5) calculated: 75.27% C, 6.71% H, 5.49% N; found: 74.89% C, 6.73% H, 5.54% N. ¹H NMR (CDCl₃): 12.15 s, 1 H (OH); 7.27–7.13 m, 6 H (H4, H6, H2', H3', H5', H6'); 6.89 d, 1 H, *J*(3,4) = 8.70 (H3); 6.64 bs, 1 H (NH); 4.45 d, 2 H, *J* = 5.40 (CH₂); 2.36 s, 3 H (CH₃); 2.25 s, 3 H (CH₃). ¹³C NMR (CDCl₃): 169.7, 159.3, 137.6, 135.1, 134.4, 129.5, 127.9, 127.7, 125.3, 118.7, 43.4, 21.0, 20.4.

3,5-Dibromo-*N*-(4-methylbenzyl)salicylamide (3f). White crystals. Yield 69%, m.p. 125–127 °C. IR: ν(C=O) 1641. For C₁₅H₁₃Br₂NO₂ (399.1) calculated: 45.14% C, 3.28% H, 3.51% N; found: 45.01% C, 3.21% H, 3.25% N. ¹H NMR (CDCl₃): 7.76 d, 1 H, *J*(4,6) = 2.10 (H6); 7.43 d, 1 H, *J*(4,6) = 2.10 (H4); 7.26–7.13 m AA' BB', 4 H (H2', H3', H5', H6'); 6.58 bs, 1 H (NH); 4.57 d, 2 H, *J* = 5.70 (CH₂); 2.36 s, 3 H (CH₃). ¹³C NMR (CDCl₃): 167.9, 127.4, 139.4, 138.0, 133.5, 129.6, 128.0, 127.3, 116.2, 113.4, 110.0, 43.9, 21.1.

4-Methoxy-*N*-(4-methylbenzyl)salicylamide (3g). White crystals. Yield 68%, m.p. 93–95 °C. IR: ν(C=O) 1645. For C₁₆H₁₇NO₃ (271.3) calculated: 70.83% C, 6.32% H, 5.16% N; found: 70.81% C, 6.26% H, 5.13% N. ¹H NMR (CDCl₃): 7.25 d overlapped, 1 H, *J*(5,6) = 8.70 (H6); 7.24–7.15 m overlapped AA' BB', 4 H (H2', H3', H5', H6'); 6.46 bs overlapped, 1 H (NH); 6.46 d overlapped, 1 H, *J*(3,5) = 2.70 (H3); 6.36 dd, 1 H, *J*(5,6) = 8.70, *J*(3,5) = 2.70 (H5); 4.56 d, 2 H, *J* = 5.40 (CH₂); 3.79 s, 3 H (OCH₃); 2.35 s, 3 H (CH₃). ¹³C NMR (CDCl₃): 169.6, 164.3, 163.8, 137.5, 134.5, 129.4, 127.8, 126.6, 107.0, 106.9, 101.5, 55.3, 43.3, 21.1.

***N*-(4-Methylbenzyl)-5-nitrosalicylamide (3h).** Yellow crystals. Yield 58%, m.p. 187–189 °C. IR: ν(C=O) 1641. For C₁₅H₁₄N₂O₄ (286.3) calculated: 62.93% C, 4.93% H, 9.79% N; found: 63.02% C, 4.85% H, 9.43% N. ¹H NMR (DMSO-*d*₆): 9.63 t, 1 H, *J* = 5.70 (NH); 8.88 d, 1 H, *J*(4,6) = 2.70 (H6); 8.23 dd, 1 H, *J*(3,4) = 9.30, *J*(4,6) = 2.70 (H4); 7.26–7.13 m AA' BB', 4 H (H2', H3', H5', H6'); 7.08 d, 1 H, *J*(3,4) = 9.30 (H3); 4.47 d, 2 H, *J* = 5.70 (CH₂); 2.25 s, 3 H (CH₃). ¹³C NMR (DMSO-*d*₆): 167.1, 165.5, 139.4, 136.4, 135.7, 129.2, 129.0, 127.7, 125.1, 118.6, 115.9, 42.7, 20.9.

4-Chloro-*N*-(4-methylbenzyl)salicylamide (3i). White crystals. Yield 71%, m.p. 162–165 °C. IR: ν(C=O) 1632. For C₁₅H₁₄ClNO₂ (275.7) calculated: 65.34% C, 5.12% H, 5.08% N; found: 65.02% C, 4.89% H, 4.96% N. ¹H NMR (DMSO-*d*₆): 9.33 t, 1 H, *J* = 6.00 (NH); 7.91 d, 1 H, *J*(5,6) = 8.40 (H6); 7.22–7.10 m AA' BB', 4 H (H2', H3', H5', H6'); 6.99 d overlapped, 1 H, *J*(3,5) = 1.80 (H3); 6.96 dd overlapped, 1 H, *J*(5,6) = 8.40, *J*(3,5) = 1.80 (H5); 4.45 d, 2 H, *J* =

6.00 (CH₂); 2.25 s, 3 H (CH₃). ¹³C NMR (DMSO-*d*₆): 168.1, 161.0, 137.9, 136.3, 135.9, 129.8, 129.1, 127.5, 119.1, 117.3, 114.7, 42.4, 20.9.

3-Methoxy-*N*-(4-methylbenzyl)salicylamide (3j). White crystals. Yield 56%, m.p. 108–110 °C. IR: ν(C=O) 1640. For C₁₆H₁₇NO₃ (271.3) calculated: 70.83% C, 6.32% H, 5.16% N; found: 70.38% C, 5.99% H, 4.95% N. ¹H NMR (CDCl₃): 11.92 s, 1 H (OH); 7.23–7.11 m AA' BB', 4 H (H2', H3', H5', H6'); 7.08 dd, 1 H, *J*(5,6) = 7.95, *J*(4,6) = 1.35 (H6); 6.97 bs overlapped, 1 H (NH); 6.95 dd overlapped, 1 H, *J*(4,5) = 7.95, *J*(4,6) = 1.35 (H4); 6.77 t, 1 H, *J*(4,5) = 7.95 (H5); 4.57 d, 2 H, *J* = 6.00 (CH₂); 3.87 s, 3 H (OCH₃); 2.33 s, 3 H (CH₃). ¹³C NMR (CDCl₃): 169.2, 150.9, 148.8, 137.4, 134.4, 129.4, 127.8, 118.2, 117.6, 114.7, 114.6, 56.0, 43.4, 21.0.

5-Methoxy-*N*-(4-methylbenzyl)salicylamide (3k). White crystals. Yield 50%, m.p. 109–110 °C. IR: ν(C=O) 1652. For C₁₆H₁₇NO₃ (271.3) calculated: 70.83% C, 6.32% H, 5.16% N; found: 70.54% C, 6.21% H, 4.95% N. ¹H NMR (CDCl₃): 11.84 s, 1 H (OH); 7.24–7.12 m AA' BB', 4 H (H2', H3', H5', H6'); 7.00 dd, 1 H, *J*(3,4) = 9.00, *J*(4,6) = 3.00 (H4); 6.90 d, 1 H, *J*(3,4) = 9.00 (H3); 6.88 d, 1 H, *J*(4,6) = 3.00 (H6); 6.77 bs, 1 H (NH); 4.56 d, 2 H, *J* = 6.00 (CH₂); 3.73 s, 3 H (OCH₃); 2.35 s, 3 H (CH₃). ¹³C NMR (CDCl₃): 169.4, 155.4, 151.7, 137.5, 134.3, 129.4, 127.8, 121.0, 119.2, 114.0, 109.7, 55.9, 43.4, 21.0.

5-Bromo-*N*-(4-fluorobenzyl)salicylamide (4b). White crystals. Yield 60%, m.p. 159–162 °C. IR: ν(C=O) 1621. For C₁₄H₁₁BrFNO₂ (324.2) calculated: 51.87% C, 3.42% H, 4.32% N; found: 51.65% C, 3.21% H, 3.81% N. ¹H NMR (DMSO-*d*₆): 9.33 t, 1 H, *J* = 6.00 (NH); 7.91 d, 1 H, *J*(4,6) = 2.40 (H6); 7.54 dd, 1 H, *J*(3,4) = 8.70, *J*(4,6) = 2.40 (H4); 7.37–7.33 m, 2 H (H2', H6'); 7.19–7.11 m, 2 H (H3', H5'); 6.90 d, 1 H, *J*(3,4) = 8.70 (H3); 4.47 d, 2 H, *J* = 6.00 (CH₂). ¹³C NMR (DMSO-*d*₆): 167.6, 161.5 (d, *J* = 241.05); 159.1, 136.4, 135.2 (d, *J* = 2.85); 130.5, 129.7 (d, *J* = 7.95); 118.0, 117.6, 115.4 (d, *J* = 21.30); 110.0, 42.1.

5-Chloro-*N*-(4-fluorobenzyl)salicylamide (4c). White crystals. Yield 61%, m.p. 155–157 °C. IR: ν(C=O) 1621. For C₁₄H₁₁ClFNO₂ (279.7) calculated: 60.12% C, 3.96% H, 5.01% N; found: 59.89% C, 3.97% H, 4.57% N. ¹H NMR (DMSO-*d*₆): 9.39 t, 1 H, *J* = 6.00 (NH); 7.96 d, 1 H, *J*(4,6) = 2.40 (H6); 7.45–7.36 m, 3 H (H4, H2', H6'); 7.19–7.11 m, 2 H (H3', H5'); 6.94 d, 1 H, *J*(3,4) = 8.70 (H3); 4.48 d, 2 H, *J* = 6.00 (CH₂). ¹³C NMR (DMSO-*d*₆): 167.6, 161.5 (d, *J* = 241.28); 158.7, 135.1 (d, *J* = 2.85); 133.6, 129.7 (d, *J* = 7.95); 127.6, 122.6, 119.6, 117.0, 115.4 (d, *J* = 21.08); 42.1.

3,5-Dichloro-*N*-(4-fluorobenzyl)salicylamide (4d). White crystals. Yield 73%, m.p. 124–126 °C. IR: ν(C=O) 1647. For C₁₄H₁₀Cl₂FNO₂ (314.1) calculated: 53.53% C, 3.21% H, 4.46% N; found: 54.12% C, 3.11% H, 4.43% N. ¹H NMR (DMSO-*d*₆): 9.70 t, 1 H, *J* = 5.70 (NH); 8.03 d, 1 H, *J*(4,6) = 2.40 (H6); 7.76 d, 1 H, *J*(4,6) = 2.40 (H4); 7.40–7.35 m, 2 H (H2', H6'); 7.19–7.12 m, 2 H (H3', H5'); 4.48 d, 2 H, *J* = 5.70 (CH₂). ¹³C NMR (DMSO-*d*₆): 168.4, 161.6 (d, *J* = 241.28); 156.0, 134.6 (d, *J* = 3.08); 133.4, 129.8 (d, *J* = 7.95); 125.9, 122.6, 122.3, 116.5, 115.4 (d, *J* = 21.38); 42.2.

***N*-(4-Fluorobenzyl)-5-methylsalicylamide (4e)**. White crystals. Yield 63%, m.p. 143.5–145 °C. IR: ν(C=O) 1644. For C₁₅H₁₄FNO₂ (259.3) calculated: 69.49% C, 5.44% H, 5.40% N; found: 69.52% C, 5.59% H, 5.49% N. ¹H NMR (DMSO-*d*₆): 12.28 s, 1 H (OH); 9.31 t, 1 H, *J* = 5.70 (NH); 7.71 d, 1 H, *J*(4,6) = 1.50 (H6); 7.39–7.34 m, 2 H (H2', H6'); 7.19 dd overlapped, 1 H, *J*(3,4) = 8.10, *J*(4,6) = 1.50 (H4); 7.18–7.12 m overlapped, 2 H (H3', H5'); 6.80 d, 1 H, *J*(3,4) = 8.10 (H3); 4.48 d, 2 H, *J* = 5.70 (CH₂); 2.23 s, 3 H (CH₃). ¹³C NMR (DMSO-*d*₆): 169.2, 161.5 (d, *J* = 240.98); 156.2, 135.5 (d, *J* = 3.15); 134.7, 129.6 (d, *J* = 7.95); 127.9, 127.5, 117.4, 115.3 (d, *J* = 21.08); 114.9, 41.9, 20.3.

3,5-Dibromo-*N*-(4-fluorobenzyl)salicylamide (4f). White crystals. Yield 69%, m.p. 135–137 °C. IR: ν(C=O) 1641. For C₁₄H₁₀Br₂FNO₂ (403.1) calculated: 41.72% C, 2.50% H, 3.48% N;

found: 41.81% C, 2.41% H, 3.29% N. ^1H NMR (DMSO- d_6): 9.71 t, 1 H, $J = 5.70$ (NH); 8.18 d, 1 H, $J(4,6) = 2.40$ (H6); 7.97 d, 1 H, $J(4,6) = 2.40$ (H4); 7.40–7.35 m, 2 H (H2', H6'); 7.19–7.12 m, 2 H (H3', H5'); 4.48 d, 2 H, $J = 5.70$ (CH_2). ^{13}C NMR (DMSO- d_6): 168.3, 161.6 (d, $J = 241.28$); 157.3, 138.8, 134.5 (d, $J = 3.08$); 129.8 (d, $J = 7.95$); 129.2, 116.8, 115.4 (d, $J = 21.08$); 112.4, 109.8, 42.3.

N-(4-Fluorobenzyl)-4-methoxysalicylamide (**4g**). White crystals. Yield 44%, m.p. 139–141 °C. IR: $\nu(\text{C}=\text{O})$ 1649. For $\text{C}_{15}\text{H}_{14}\text{FNO}_3$ (275.3) calculated: 65.45% C, 5.13% H, 5.09% N; found: 65.02% C, 4.96% H, 4.95% N. ^1H NMR (DMSO- d_6): 9.21 t, 1 H, $J = 6.00$ (NH); 7.96 (d, 1 H, $J(5,6) = 9.00$ (H6)); 7.37–7.32 m, 2 H (H2', H6'); 7.18–7.12 m, 2 H (H3', H5'); 6.47 dd, 1 H, $J(5,6) = 9.00$, $J(3,5) = 2.70$ (H5); 6.42 d, 1 H, $J(3,5) = 2.70$ (H3); 4.46 d, 2 H, $J = 6.00$ (CH_2); 3.76 s, 3 H (OCH_3). ^{13}C NMR (DMSO- d_6) 169.4, 163.9, 162.9, 161.5 (d, $J = 240.75$); 135.5 (d, $J = 2.85$); 129.5 (d, $J = 7.95$); 129.0, 115.3 (d, $J = 21.08$); 107.8, 106.4, 101.4, 55.6, 41.8.

N-(4-Fluorobenzyl)-5-nitrosalicylamide (**4h**). Yellow crystals. Yield 58%, m.p. 193–195 °C. IR: $\nu(\text{C}=\text{O})$ 1651. For $\text{C}_{14}\text{H}_{11}\text{FN}_2\text{O}_4$ (290.3) calculated: 62.93% C, 4.93% H, 9.79% N; found: 62.45% C, 4.78% H, 9.56% N. ^1H NMR (DMSO- d_6): 9.68 t, 1 H, $J = 6.00$ (NH); 8.86 d, 1 H, $J(4,6) = 2.70$ (H6); 8.25 dd, 1 H, $J(3,4) = 9.00$, $J(4,6) = 2.70$ (H4); 7.41–7.36 m, 2 H (H2', H6'); 7.19–7.12 m overlapped, 2 H (H3', H5'); 7.09 d overlapped, 1 H, $J(3,4) = 9.00$ (H3); 4.51 d, 2 H, $J = 6.00$ (CH_2). ^{13}C NMR (DMSO- d_6): 166.9, 165.5, 161.5 (d, $J = 240.98$); 139.3, 135.0 (d, $J = 2.78$); 129.7 (d, $J = 7.95$); 129.0, 125.3, 118.7, 116.2, 115.3 (d, $J = 21.38$); 42.2.

4-Chloro-*N*-(4-fluorobenzyl)salicylamide (**4i**). White crystals. Yield 52%, m.p. 153–154.5 °C. IR: $\nu(\text{C}=\text{O})$ 1632. For $\text{C}_{14}\text{H}_{11}\text{ClFNO}_2$ (279.7) calculated: 60.12% C, 3.96% H, 5.01% N; found: 59.98% C, 4.03% H, 5.05% N. ^1H NMR (DMSO- d_6): 9.36 t, 1 H, $J = 6.00$ (NH); 7.96 d, 1 H, $J(5,6) = 8.40$ (H6); 7.38–7.33 m, 2 H (H2', H6'); 7.18–7.12 m, 2 H (H3', H5'); 7.00–6.95 m, 2 H (H3, H5); 4.48 d, 2 H, $J = 6.00$ (CH_2). ^{13}C NMR (DMSO- d_6): 168.1, 161.5 (d, $J = 240.05$); 160.8, 137.9, 135.2 (d, $J = 3.15$); 129.9, 129.6 (d, $J = 7.95$); 119.2, 117.2, 115.4 (d, $J = 21.08$); 114.8, 42.0.

N-(4-Fluorobenzyl)-3-methoxysalicylamide (**4j**). White crystals. Yield 53%, m.p. 104–105 °C. IR: $\nu(\text{C}=\text{O})$ 1641. For $\text{C}_{15}\text{H}_{14}\text{FNO}_3$ (275.3) calculated: 65.45% C, 5.13% H, 5.09% N; found: 65.64% C, 5.25% H, 5.02% N. ^1H NMR (DMSO- d_6): 9.37 t, 1 H, $J = 6.00$ (NH); 7.45 d, 1 H, $J = 8.40$ (H6); 7.37–7.32 m, 2 H (H2', H6'); 7.18–7.09 m, 3 H (H4, H3', H5'); 6.85–6.78 m, 1 H (H5); 4.48 d, 2 H, $J = 6.00$ (CH_2); 3.77 s, 3 H (OCH_3). ^{13}C NMR (DMSO- d_6): 169.6, 161.5 (d, $J = 240.98$); 151.0, 148.7, 135.3 (d, $J = 3.15$); 129.6 (d, $J = 7.95$); 118.8, 118.1, 115.7, 115.3 (d, $J = 21.08$); 115.0, 56.0, 41.9.

N-(4-Fluorobenzyl)-5-methoxysalicylamide (**4k**). White crystals. Yield 43%, m.p. 119–120 °C. IR: $\nu(\text{C}=\text{O})$ 1650. For $\text{C}_{15}\text{H}_{14}\text{FNO}_3$ (291.7) calculated: 65.45% C, 5.13% H, 5.09% N; found: 65.02% C, 4.98% H, 4.89% N. ^1H NMR (DMSO- d_6): 11.98 s, 1 H (OH); 9.32 t, 1 H, $J = 6.00$ (NH); 7.44 d, 1 H, $J(4,6) = 3.00$ (H6); 7.39–7.34 m, 2 H (H2', H6'); 7.18–7.12 m, 2 H (H3', H5'); 7.02 dd, 1 H, $J(3,4) = 9.00$, $J(4,6) = 3.00$ (H4); 6.84 d, 1 H, $J(3,4) = 9.00$ (H3); 4.49 d, 2 H, $J = 6.00$ (CH_2); 3.72 s, 3 H (OCH_3). ^{13}C NMR (DMSO- d_6): 168.8, 161.5 (d, $J = 240.98$); 154.2, 151.8, 135.4 (d, $J = 2.85$); 129.6 (d, $J = 7.95$); 121.3, 118.5 (two peaks overlapped); 115.3 (d, $J = 21.38$); 111.3, 55.9, 41.9.

5-Bromo-*N*-(3,4-dichlorobenzyl)salicylamide (**5b**). White crystals. Yield 51%, m.p. 168–171 °C (ref.⁷ 160–161 °C). IR: $\nu(\text{C}=\text{O})$ 1623. ^1H NMR (DMSO- d_6): 12.32 s, 1 H (OH); 9.37 t, 1 H, $J = 5.70$ (NH); 8.04 d, 1 H, $J(4,6) = 2.40$ (H6); 7.60–7.52 m, 3 H (H4, H2', H5'); 7.32 dd, 1 H, $J(5',6') = 8.25$, $J(2',6') = 2.10$ (H6'); 6.90 d, 1 H, $J(3,4) = 8.55$ (H3); 4.48 d, 2 H, $J = 5.70$ (CH_2). ^{13}C NMR (DMSO- d_6): 167.5, 158.8, 140.3, 136.4, 131.1, 130.8, 130.7, 129.7, 129.6, 128.0, 119.9, 117.8, 110.0, 41.8.

5-Chloro-N-(3,4-dichlorobenzyl)salicylamide (5c). White crystals. Yield 67%, m.p. 158–161 °C (ref.⁷ 154–156 °C). IR: $\nu(\text{C=O})$ 1619. ¹H NMR (DMSO-*d*₆): 12.28 s, 1 H (OH); 9.37 t, 1 H, *J* = 6.00 (NH); 7.93 d, 1 H, *J*(4,6) = 2.55 (H6); 7.60–7.57 m, 2 H (H2', H5'); 7.44 dd, 1 H, *J*(3,4) = 8.85, *J*(4,6) = 2.55 (H4); 7.32 dd, 1 H, *J*(5',6') = 8.40, *J*(2',6') = 2.10 (H6'); 6.95 d, 1 H, *J*(3,4) = 8.85 (H3); 4.49 d, 2 H, *J* = 6.00 (CH₂). ¹³C NMR (DMSO-*d*₆): 167.5, 158.4, 140.3, 133.5, 131.1, 130.8, 129.7, 129.6, 128.0, 127.8, 122.7, 119.5, 117.3, 41.8.

N-(3,4-dichlorobenzyl)-3,5-dichlorosalicylamide (5d). White crystals. Yield 56%, m.p. 149–151 °C (ref.³ m.p. was not published). IR: $\nu(\text{C=O})$ 1644. For C₁₄H₉Cl₄NO₂ (330.6) calculated: 46.06% C, 2.49% H, 3.84% N; found: 46.29% C, 2.31% H, 3.56% N. ¹H NMR (DMSO-*d*₆): 9.70 t, 1 H, *J* = 5.70 (NH); 8.00 d, 1 H, *J*(4,6) = 2.40 (H6); 7.77 d, 1 H, *J*(4,6) = 2.40 (H4); 7.61–7.57 m, 2 H (H2', H5'); 7.32 dd, 1 H, *J*(5',6') = 8.10, *J*(2',6') = 2.10 (H6'); 4.50 d, 2 H, *J* = 5.70 (CH₂). ¹³C NMR (DMSO-*d*₆): 168.5, 155.9, 139.6, 133.4, 131.2, 130.8, 129.9, 129.8, 128.0, 126.0, 122.6, 122.3, 116.5, 41.9.

N-(3,4-dichlorobenzyl)-5-methylsalicylamide (5e). White crystals. Yield 71%, m.p. 141–142.5 °C. IR: $\nu(\text{C=O})$ 1647. For C₁₅H₁₃Cl₂NO₂ (310.2) calculated: 58.08% C, 4.22% H, 4.52% N; found: 57.78% C, 3.98% H, 4.32% N. ¹H NMR (DMSO-*d*₆): 12.07 s, 1 H (OH); 9.30 t, 1 H, *J* = 6.00 (NH); 7.68 d, 1 H, *J*(4,6) = 1.80 (H6); 7.60–7.56 m, 2 H (H2', H5'); 7.31 dd, 1 H, *J*(5',6') = 8.40, *J*(2',6') = 2.10 (H6'); 7.20 dd, 1 H, *J*(3,4) = 8.40, *J*(4,6) = 1.80 (H4); 6.81 d, 1 H, *J*(3,4) = 8.40 (H3); 4.48 d, 2 H, *J* = 6.00 (CH₂); 2.23 s, 3 H (CH₃). ¹³C NMR (DMSO-*d*₆): 169.1, 127.9, 140.6, 134.7, 131.1, 130.8, 129.6, 129.6, 128.0, 127.9, 127.6, 117.4, 115.0, 41.6, 20.3.

3,5-Dibromo-N-(3,4-dichlorobenzyl)salicylamide (5f). White crystals. Yield 67%, m.p. 155–157 °C (ref.¹¹ 157–160 °C). IR: $\nu(\text{C=O})$ 1641. For C₁₄H₉Br₂Cl₂NO₂ (453.9) calculated: 37.04% C, 2.00% H, 3.09% N; found: 36.89% C, 2.11% H, 3.23% N. ¹H NMR (DMSO-*d*₆): 9.71 t, 1 H, *J* = 5.70 (NH); 8.16 d, 1 H, *J*(4,6) = 2.25 (H6); 7.95 d, 1 H, *J*(4,6) = 2.25 (H4); 7.61–7.56 m, 2 H (H2', H5'); 7.32 dd, 1 H, *J*(5',6') = 8.40, *J*(2',6') = 2.10 (H6'); 4.49 d, 2 H, *J* = 5.70 (CH₂). ¹³C NMR (DMSO-*d*₆): 168.4, 157.2, 139.6, 138.8, 131.2, 130.8, 129.9, 129.8, 129.3, 128.1, 116.7, 112.4, 109.8, 41.9.

N-(3,4-Dichlorobenzyl)-4-methoxysalicylamide (5g). White crystals. Yield 58%, m.p. 119–119.5 °C. IR: $\nu(\text{C=O})$ 1639. For C₁₅H₁₃Cl₂NO₃ (326.2) calculated: 55.23% C, 4.02% H, 4.29% N; found: 54.95% C, 3.97% H, 4.26% N. ¹H NMR (DMSO-*d*₆): 9.21 t, 1 H, *J* = 6.30 (NH); 7.81 d, 1 H, *J*(5,6) = 8.85 (H6); 7.59–7.54 m, 2 H (H2', H5'); 7.30 dd, 1 H, *J*(5',6') = 8.10, *J*(2',6') = 1.80 (H6'); 6.48 dd, 1 H, *J*(5,6) = 8.85, *J*(3,5) = 2.55 (H5); 6.43 d, 1 H, *J*(3,5) = 2.55 (H3); 4.47 d, 2 H, *J* = 6.30 (CH₂); 3.76 s, 3 H (OCH₃). ¹³C NMR (DMSO-*d*₆): 169.5, 163.9, 162.7, 140.7, 131.1, 130.8, 129.6, 129.5, 129.2, 127.9, 107.8, 106.4, 101.4, 55.6, 41.5.

N-(3,4-Dichlorobenzyl)-5-nitrosalicylamide (5h). Yellow crystals. Yield 60%, m.p. 191.5–193 °C. IR: $\nu(\text{C=O})$ 1648. For C₁₄H₁₀Cl₂N₂O₄ (341.2) calculated: 49.29% C, 2.95% H, 8.21% N; found: 48.95% C, 3.05% H, 8.29% N. ¹H NMR (DMSO-*d*₆): 9.58 t, 1 H, *J* = 6.00 (NH); 8.81 d, 1 H, *J*(4,6) = 2.70 (H6); 8.24 dd, 1 H, *J*(3,4) = 9.00, *J*(4,6) = 2.70 (H4); 7.63–7.53 m, 2 H (H2', H5'); 7.34 dd, 1 H, *J*(5',6') = 8.40, *J*(2',6') = 2.10 (H6'); 7.09 d, 1 H, *J*(3,4) = 9.00 (H3); 4.50 d, 2 H, *J* = 6.00 (CH₂). ¹³C NMR (DMSO-*d*₆): 166.9, 165.0, 140.1, 139.5, 131.2, 130.7, 129.8, 129.7, 128.9, 128.0, 125.3, 118.5, 116.4, 41.9.

4-Chloro-N-(3,4-dichlorobenzyl)salicylamide (5i). White crystals. Yield 80%, m.p. 154–155 °C. IR: $\nu(\text{C=O})$ 1629. For C₁₄H₁₀Cl₃NO₂ (330.6) calculated: 50.86% C, 3.05% H, 4.24% N; found: 50.68% C, 3.21% H, 4.36% N. ¹H NMR (DMSO-*d*₆): 9.35 t, 1 H, *J* = 6.00 (NH); 7.87 d, 1 H, *J*(5,6) = 8.70 (H6); 7.59–7.55 m, 2 H (H2', H5'); 7.31 dd, 1 H, *J*(5',6') = 8.40, *J*(2',6') = 2.10 (H6'); 7.00–6.94 m, 2 H (H3, H5); 4.49 d, 2 H, *J* = 6.00 (CH₂). ¹³C NMR (DMSO-*d*₆): 168.0, 160.5, 140.4, 137.9, 131.1, 130.7, 130.1, 129.7, 129.6, 127.9, 119.2, 117.2, 115.0, 41.7.

N-(3,4-Dichlorobenzyl)-3-methoxysalicylamide (**5j**). White crystals. Yield 42%, m.p. 144–146 °C. IR: $\nu(\text{C}=\text{O})$ 1635. For $\text{C}_{15}\text{H}_{13}\text{Cl}_2\text{NO}_3$ (291.7) calculated: 55.23% C, 4.02% H, 4.29% N; found: 55.01% C, 4.11% H, 4.21% N. ^1H NMR ($\text{DMSO}-d_6$): 12.45 s, 1 H (OH); 9.38 t, 1 H, $J = 6.00$ (NH); 7.60–7.55 m, 2 H (H2', H5'); 7.44 dd, 1 H, $J(5,6) = 7.95$, $J(4,6) = 1.80$ (H6); 7.31 dd, 1 H, $J(5',6') = 8.40$, $J(2',6') = 2.10$ (H6'); 7.11 dd, 1 H, $J(4,5) = 7.95$, $J(4,6) = 1.80$ (H4); 6.82 t, 1 H, $J(4,5) = 7.95$ (H5); 4.48 d, 2 H, $J = 6.00$ (CH_2); 3.77 s, 3 H (OCH_3). ^{13}C NMR ($\text{DMSO}-d_6$): 169.7, 150.8, 148.7, 140.4, 131.1, 130.8, 129.7, 129.5, 127.9, 118.9, 118.2, 115.7, 115.0, 56.0, 41.6.

N-(3-Chlorobenzyl)-5-methoxysalicylamide (**5k**). White crystals. Yield 49%, m.p. 113.5–115 °C. IR: $\nu(\text{C}=\text{O})$ 1637. For $\text{C}_{15}\text{H}_{14}\text{ClNO}_3$ (291.7) calculated: 61.76% C, 4.84% H, 4.80% N; found: 61.77% C, 4.97% H, 4.85% N. ^1H NMR ($\text{DMSO}-d_6$): 11.93 s, 1 H (OH); 9.36 t, 1 H, $J = 6.00$ (NH); 7.46 d, 1 H, $J(4,6) = 3.00$ (H6); 7.39–7.26 m, 4 H (H2', H4', H5', H6'); 7.02 dd, 1 H, $J(3,4) = 9.00$, $J(4,6) = 3.00$ (H4); 6.86 d, 1 H, $J(3,4) = 9.00$ (H3); 4.52 d, 2 H, $J = 6.00$ (CH_2); 3.73 s, 3 H (OCH_3). ^{13}C NMR ($\text{DMSO}-d_6$): 168.8, 154.1, 151.8, 141.9, 133.3, 130.5, 127.4, 127.1, 126.2, 121.3, 118.5, 115.2, 111.4, 55.9, 42.1.

5-Bromo-*N*-(4-methoxybenzyl)salicylamide (**6b**). White crystals. Yield 74%, m.p. 122–126 °C. IR: $\nu(\text{C}=\text{O})$ 1640. For $\text{C}_{15}\text{H}_{14}\text{BrNO}_3$ (336.2) calculated: 53.59% C, 4.20% H, 4.17% N; found: 53.50% C, 4.03% H, 4.19% N. ^1H NMR (CDCl_3): 12.28 s, 1 H (OH); 7.47–7.40 m, 2 H (H4, H6); 7.28–7.23 m, 2 H (H2', H6'); 6.92–6.84 m, 3 H (H3, H3', H5'); 6.63 bs, 1 H (NH); 4.55 d, 2 H, $J = 5.70$ (CH_2); 3.80 s, 3 H (OCH_3). ^{13}C NMR (CDCl_3): 168.5, 160.5, 159.3, 136.9, 129.4, 129.0, 127.0, 120.4, 115.7, 114.2, 110.2, 55.3, 43.3.

5-Chloro-*N*-(4-methoxybenzyl)salicylamide (**6c**). White crystals. Yield 63%, m.p. 134–136 °C. IR: $\nu(\text{C}=\text{O})$ 1643. For $\text{C}_{15}\text{H}_{14}\text{ClNO}_3$ (291.7) calculated: 61.76% C, 4.84% H, 4.80% N; found: 61.56% C, 4.71% H, 4.85% N. ^1H NMR (CDCl_3): 12.25 s, 1 H (OH); 7.35–7.29 m, 2 H (H4, H6); 7.28–7.22 m, 2 H (H2', H6'); 6.94–6.85 m, 3 H (H3, H3', H5'); 6.65 bs, 1 H (NH); 4.54 d, 2 H, $J = 5.70$ (CH_2); 3.80 s, 3 H (OCH_3). ^{13}C NMR (CDCl_3): 168.6, 160.0, 159.3, 134.1, 129.4, 129.0, 125.0, 123.3, 120.1, 115.0, 114.3, 55.3, 43.3.

3,5-Dichloro-*N*-(4-methoxybenzyl)salicylamide (**6d**). White crystals. Yield 62%, m.p. 121–124 °C. IR: $\nu(\text{C}=\text{O})$ 1642. For $\text{C}_{15}\text{H}_{13}\text{Cl}_2\text{NO}_3$ (326.2) calculated: 55.23% C, 4.02% H, 4.29% N; found: 55.02% C, 4.03% H, 4.22% N. ^1H NMR (CDCl_3): 7.46 d, 1 H, $J(4,6) = 2.40$ (H6); 7.27 d overlapped, 1 H, $J(4,6) = 2.40$ (H4); 7.27–7.21 m overlapped, 2 H (H2', H6'); 6.91–6.85 m, 2 H (H3', H5'); 6.57 bs, 1 H (NH); 4.54 d, 2 H, $J = 5.70$ (CH_2); 3.79 s, 3 H (OCH_3). ^{13}C NMR (CDCl_3): 168.0, 159.4, 156.0, 133.8, 129.4, 128.6, 124.0, 123.7, 123.0, 115.8, 114.3, 55.3, 43.6.

N-(4-Methoxybenzyl)-5-methylsalicylamide (**6e**). White crystals. Yield 62%, m.p. 113–115 °C. IR: $\nu(\text{C}=\text{O})$ 1644. For $\text{C}_{16}\text{H}_{17}\text{NO}_3$ (271.3) calculated: 70.83% C, 6.32% H, 5.16% N; found: 70.89% C, 6.40% H, 5.20% N. ^1H NMR (CDCl_3): 12.15 s, 1 H (OH); 7.31–7.24 m, 2 H (H2', H6'); 7.19 dd, 1 H, $J(3,4) = 8.10$, $J(4,6) = 2.10$ (H4); 7.11 d, 1 H, $J(4,6) = 2.10$ (H6); 6.93–6.85 m, 3 H (H3, H3', H5'); 6.56 bs, 1 H (NH); 4.54 d, 2 H, $J = 5.70$ (CH_2); 3.80 s, 3 H (OCH_3). ^{13}C NMR (CDCl_3): 169.7, 159.4, 159.2, 135.1, 129.5, 129.3, 127.7, 125.3, 118.3, 114.2, 113.7, 55.3, 43.1, 20.4.

3,5-Dibromo-*N*-(4-methoxybenzyl)salicylamide (**6f**). White crystals. Yield 50%, m.p. 121–124 °C. IR: $\nu(\text{C}=\text{O})$ 1636. For $\text{C}_{15}\text{H}_{13}\text{Br}_2\text{NO}_3$ (415.1) calculated: 43.40% C, 3.16% H, 3.37% N; found: 43.02% C, 3.05% H, 3.25% N. ^1H NMR (CDCl_3): 7.75 d, 1 H, $J(4,6) = 2.10$ (H6); 7.44 d, 1 H, $J(4,6) = 2.10$ (H4); 7.28–7.21 m, 2 H (H2', H6'); 6.91–6.85 m, 2 H (H3', H5'); 6.62 bs, 1 H (NH); 4.54 d, 2 H, $J = 5.70$ (CH_2); 3.80 s, 3 H (OCH_3). ^{13}C NMR (CDCl_3): 167.9, 159.4, 157.4, 139.3, 129.4, 128.6, 127.3, 116.2, 114.3, 113.4, 110.0, 55.3, 43.6.

4-Methoxy-*N*-(4-methoxybenzyl)salicylamide (6g). White crystals. Yield 56%, m.p. 103–106 °C. IR: $\nu(\text{C}=\text{O})$ 1646. For $\text{C}_{16}\text{H}_{17}\text{NO}_4$ (287.3) calculated: 66.89% C, 5.96% H, 4.88% N; found: 66.70% C, 6.16% H, 4.57% N. ^1H NMR (CDCl_3): 7.28–7.23 m overlapped, 2 H ($\text{H}2'$, $\text{H}6'$); 7.23 d overlapped, 1 H, $J(5,6) = 9.00$ ($\text{H}6$); 6.91–6.85 m, 2 H ($\text{H}3'$, $\text{H}5'$); 6.46 d, 1 H, $J(3,5) = 2.40$ ($\text{H}3$); 6.40–6.33 m, 2 H ($\text{H}5$, NH); 4.54 d, 2 H, $J = 5.40$ (CH_2); 3.80 s, 3 H (OCH'_3); 3.79 s, 3 H (OCH_3). ^{13}C NMR (CDCl_3): 169.6, 164.3, 163.9, 159.2, 129.6, 129.3, 126.5, 114.2, 107.0, 106.9, 101.5, 55.4, 55.3, 43.0.

***N*-(4-Methoxybenzyl)-5-nitrosalicylamide (6h).** Yellow crystals. Yield 42%, m.p. 137–140 °C. IR: $\nu(\text{C}=\text{O})$ 1648. For $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_5$ (302.3) calculated: 59.6% C, 4.67% H, 9.27% N; found: 59.23% C, 4.64% H, 9.08% N. ^1H NMR (CDCl_3): 8.41 d, 1 H, $J(4,6) = 2.70$ ($\text{H}6$); 8.25 dd, 1 H, $J(3,4) = 9.30$, $J(4,6) = 2.70$ ($\text{H}4$); 7.33–7.36 m, 2 H ($\text{H}2'$, $\text{H}6'$); 7.06 d, 1 H, $J(3,5) = 9.30$ ($\text{H}3$); 6.98 bs, 1 H (NH); 6.92–6.86 m, 2 H ($\text{H}3'$, $\text{H}5'$); 4.59 d, 2 H, $J = 5.70$ (CH_2); 3.80 s, 3 H (OCH'_3). ^{13}C NMR (CDCl_3): 168.2, 167.3, 159.5, 139.1, 129.6, 129.3, 128.7, 122.4, 119.4, 114.3, 113.6, 55.3, 43.5.

4-Chloro-*N*-(4-methoxybenzyl)salicylamide (6i). White crystals. Yield 38%, m.p. 114–118 °C. IR: $\nu(\text{C}=\text{O})$ 1632. For $\text{C}_{15}\text{H}_{14}\text{ClNO}_3$ (291.7) calculated: 61.76% C, 4.84% H, 4.80% N; found: 61.56% C, 4.85% H, 4.76% N. ^1H NMR (CDCl_3): 12.55 s, 1 H (OH); 7.28–7.21 m, 3 H ($\text{H}6$, $\text{H}2'$, $\text{H}6'$); 7.00 d, 1 H, $J(3,5) = 1.80$ ($\text{H}3$); 6.91–6.85 m, 2 H ($\text{H}3'$, $\text{H}5'$); 6.78 dd, 1 H, $J(5,6) = 8.40$, $J(3,5) = 2.25$ ($\text{H}5$); 6.68 bs, 1 H (NH); 4.54 d, 2 H, $J = 5.40$ (CH_2); 3.80 s, 3 H (OCH'_3). ^{13}C NMR (CDCl_3): 169.0, 162.4, 159.3, 139.8, 129.4, 129.1, 126.3, 119.1, 118.7, 114.3, 112.6, 55.3, 43.3.

3-Methoxy-*N*-(4-methoxybenzyl)salicylamide (6j). White crystals. Yield 56%, m.p. 103–104 °C. IR: $\nu(\text{C}=\text{O})$ 1644. For $\text{C}_{16}\text{H}_{17}\text{NO}_4$ (287.3) calculated: 66.89% C, 5.96% H, 4.88% N; found: 66.79% C, 5.99% H, 4.75% N. ^1H NMR (CDCl_3): 11.90 s, 1 H (OH); 7.28–7.21 m, 2 H ($\text{H}2'$, $\text{H}6'$); 7.06 dd, 1 H, $J(5,6) = 8.10$, $J(4,6) = 1.20$ ($\text{H}6$); 6.95 dd overlapped, 1 H, $J(4,5) = 8.10$, $J(4,6) = 1.20$ ($\text{H}4$); 6.92 bs overlapped, 1 H (NH); 6.88–6.83 m, 2 H ($\text{H}3'$, $\text{H}5'$); 6.76 t, 1 H, $J(4,5) = 8.10$ ($\text{H}5$); 4.54 d, 2 H, $J = 5.70$ (CH_2); 3.81 s, 3 H (OCH'_3); 3.76 s, 3 H (OCH_3). ^{13}C NMR (CDCl_3): 169.2, 159.1, 150.9, 148.8, 129.5, 129.2, 118.2, 117.6, 114.8, 114.6, 114.1, 56.0, 55.2, 43.1.

5-Methoxy-*N*-(4-methoxybenzyl)salicylamide (6k). White crystals. Yield 33%, m.p. 84.5–86 °C. IR: $\nu(\text{C}=\text{O})$ 1638. For $\text{C}_{16}\text{H}_{17}\text{NO}_4$ (287.3) calculated: 66.89% C, 5.96% H, 4.88% N; found: 66.57% C, 6.21% H, 4.77% N. ^1H NMR (CDCl_3): 11.79 s, 1 H (OH); 7.31–7.24 m, 2 H ($\text{H}2'$, $\text{H}6'$); 7.02 dd, 1 H, $J(3,4) = 9.00$, $J(4,6) = 3.00$ ($\text{H}4$); 6.93 d overlapped, 1 H, $J(3,4) = 9.00$ ($\text{H}3$); 6.92–6.87 m overlapped, 2 H ($\text{H}3'$, $\text{H}5'$); 6.79 d, 1 H, $J(4,6) = 3.00$ ($\text{H}6$); 6.46 bs, 1 H (NH); 4.54 d, 2 H, $J = 5.70$ (CH_2); 3.81 s, 3 H (OCH'_3); 3.75 s, 3 H (OCH_3). ^{13}C NMR (CDCl_3): 169.4, 159.3, 155.6, 151.7, 129.4 (two peaks overlapped); 121.0, 119.3, 114.2, 113.9, 109.7, 56.1, 55.3, 43.2.

Microbiological Tests

The following strains, obtained from the Czech National Collection of Type Cultures (CNCTC); National Institute of Public Health, Prague, were used for the evaluation of *in vitro* antimycobacterial activity: *M. tuberculosis* CNCTC My 331/8, *M. kansasii* CNCTC My 235/80, and *M. avium* CNCTC My 330/88. Activity against the clinical isolate of *Mycobacterium kansasii* 6 509/96 was (in equations $\text{MIC}_{(\text{kans. clin.})}$) tested, as well. The antimycobacterial activity of the compounds was determined in the Šula semisynthetic medium (SEVAC, Prague). This medium (with bovine serum) is routinely used in the Czech Republic. Each

strain was simultaneously inoculated into a Petri dish containing the Lowenstein-Jensen medium for the control of the sterility of the inoculum and its growth. The compounds were added to the medium in DMSO solutions. The final concentrations were 1000, 500, 250, 125, 62.5, 31, 16, 8, 4, 2 $\mu\text{mol/l}$. The MICs were determined after incubation at 37 $^\circ\text{C}$ for 14 and 21 days (see Table I). MIC was the lowest concentration of an antimycobacterially effective substance (on the above concentration scale); at which inhibition of the growth of the Mycobacteria occurred.

Calculations

All calculations were carried out using the Multireg H programme (Klemera) for Microsoft Excel. The values of the Hammett constants (Table II) were taken from ref.¹²

RESULTS AND DISCUSSION

The classical Hansch-type equation, using the squared hydrophobic parameters, was not statistically significant. In studying the relationship between the structure and antimycobacterial activity, a combination of the Hansch and Free-Wilson approaches was used. The Hansch substituent constants of hydrophobicity π of the substituents on the benzyl ring served as one parameter. The influence of their electronic parameters was not statistically significant. However, the influence of the substituents from the acyl part of the molecule appeared to be more complex, and hence we expressed them with indicator parameters (I_n) for each substituent. We have calculated several hundred equations. In this paper, we present only the most statistically significant ones. The QSAR study of the antimycobacterial activity of salicylamides includes the results obtained both after 21 days of incubation

TABLE II
Substituents constants

Substituent	σ_m	σ_p	π_m	π_m^-	π_p	π_p^-
H	0	0	0	0	0	0
Br	0.39	0.23	0.96	1.17	1.19	1.13
Cl	0.37	0.23	0.77	1.04	0.73	0.93
NO ₂	0.71	0.78	-0.05	0.54	0.02	0.45
CH ₃	-0.07	-0.17	0.52	0.50	0.60	0.48
OCH ₃	0.12	-0.27	0.12	0.12	-0.03	-0.12
F	0.34	0.06	0.22	0.47	0.15	0.31

The values of the substituent constants were taken from ref.¹²

and 14 days of incubation (see Eqs (1)–(8)), for values of I_n (see Table III). Because the activities after 21 days incubation are generally lower compared to those after 14 days incubation, the effect of the compounds is tuberculo-static. The antimycobacterial activity against *M. tuberculosis* and *M. kansasii* increased with the increase in hydrophobicity (lipophilicity) of the substituents in the benzyl moiety (see Eqs (1)–(6)); but the structure–activity relationships for *M. avium* were parabolic ($\pi_{opt} = 1.10$ – 1.15).

$$\log \text{MIC}_{(M.tuber. 14d)} = -0.268(\pm 0.056) \pi + \Sigma I_n + 2.078(\pm 0.103) \quad (1)$$

$$r = 0.819 \quad s = 0.218 \quad n = 56 \quad F = 8.13$$

TABLE III
Regression coefficients of indicator parameters I_n in Eqs (1)–(8)

Equations (1)–(8)	<i>M. tuber.</i> 14 d	<i>M. tuber.</i> 21 d	<i>M. kans.</i> 14 d	<i>M. kans.</i> 21 d	<i>M. kans.</i> <i>clin.</i> 14 d	<i>M. kans.</i> <i>clin.</i> 21 d	<i>M.</i> <i>avium.</i> 14 d	<i>M.</i> <i>avium.</i> 21 d
I(5-Br)	-0.491 (±0.146)	-0.387 (±0.111)	-0.302 (±0.105)	-0.507 (±0.127)	-0.179 (±0.102)	-0.360 (±0.112)	-0.200 (±0.109)	-0.343 (±0.102)
I(5-Cl)	-0.346 (±0.132)	-0.357 (±0.105)	-0.292 (±0.105)	-0.359 (±0.127)	-0.179 (±0.102)	-0.396 (±0.112)	-0.258 (±0.109)	-0.343 (±0.102)
I(3,5-Cl ₂)	-0.345 (±0.132)	-0.259 (±0.100)	-0.052 (±0.095)	-0.261 (±0.117)	0.052 (±0.098)	-0.112 (±0.104)	-0.246 (±0.103)	0.049 (±0.097)
I(5-CH ₃)	-0.165 (±0.146)	-0.507 (±0.181)	-0.162 (±0.131)	-0.055 (±0.151)	-0.028 (±0.119)	-0.255 (±0.169)	-0.082 (±0.116)	-0.109 (±0.119)
I(3,5-Br ₂)	-0.345 (±0.132)	-0.453 (±0.100)	0.249 (±0.095)	-0.361 (±0.117)	-0.196 (±0.098)	-0.263 (±0.104)	0.146 (±0.103)	-0.052 (±0.097)
I(4-OCH ₃)	-0.128 (±0.138)	-0.409 (±0.121)	-0.048 (±0.114)	-0.055 (±0.151)	0.016 (±0.118)	-0.153 (±0.120)	0.191 (±0.109)	-0.005 (±0.109)
I(5-NO ₂)	-0.445 (±0.132)	-0.503 (±0.100)	0.199 (±0.095)	0.091 (±0.117)	0.203 (±0.098)	0.289 (±0.104)	0.878 (±0.109)	0.735 (±0.102)
I(4-Cl)	-0.450 (±0.138)	-0.437 (±0.104)	-0.204 (±0.099)	-0.354 (±0.121)	-0.211 (±0.102)	-0.360 (±0.112)	-0.106 (±0.109)	-0.301 (±0.102)
I(3-OCH ₃)	0.116 (±0.146)	0.170 (±0.111)	0.223 (±0.105)	0.237 (±0.127)	0.268 (±0.108)	0.258 (±0.112)	0.422 (±0.116)	0.490 (±0.119)
I(5-OCH ₃)	0.219 (±0.139)	0.300 (±0.121)	-0.176 (±0.095)	-0.277 (±0.121)	0.041 (±0.103)	0.061 (±0.108)	0.095 (±0.104)	0.213 (±0.109)

$$\log \text{MIC}_{(M.tuber. 21d)} = -0.180(\pm 0.047) \pi + \Sigma \mathbf{I}_n + 2.143(\pm 0.079) \quad (2)$$

$$\mathbf{r} = 0.889 \quad \mathbf{s} = 0.165 \quad \mathbf{n} = 48 \quad \mathbf{F} = 12.3$$

$$\log \text{MIC}_{(M.kans. 14d)} = -0.224(\pm 0.044) \pi + \Sigma \mathbf{I}_n + 2.105(\pm 0.074) \quad (3)$$

$$\mathbf{r} = 0.845 \quad \mathbf{s} = 0.156 \quad \mathbf{n} = 51 \quad \mathbf{F} = 8.9$$

$$\log \text{MIC}_{(M.kans. 21d)} = -0.232(\pm 0.046) \pi + \Sigma \mathbf{I}_n + 2.323(\pm 0.099) \quad (4)$$

$$\mathbf{r} = 0.879 \quad \mathbf{s} = 0.165 \quad \mathbf{n} = 45 \quad \mathbf{F} = 11.6$$

$$\log \text{MIC}_{(M.kans.clin. 14d)} = -0.267(\pm 0.044) \pi + \Sigma \mathbf{I}_n + 2.0765(\pm 0.077) \quad (5)$$

$$\mathbf{r} = 0.838 \quad \mathbf{s} = 0.161 \quad \mathbf{n} = 53 \quad \mathbf{F} = 8.8$$

$$\log \text{MIC}_{(M.kans.clin. 21d)} = -0.245(\pm 0.042) \pi + \Sigma \mathbf{I}_n + 2.229(\pm 0.088) \quad (6)$$

$$\mathbf{r} = 0.918 \quad \mathbf{s} = 0.147 \quad \mathbf{n} = 46 \quad \mathbf{F} = 16.5$$

$$\log \text{MIC}_{(M.avium 14d)} = -0.946(\pm 0.139) \pi + 0.411(\pm 0.094) \pi^2 + \Sigma \mathbf{I}_n + 1.999(\pm 0.078) \quad (7)$$

$$\mathbf{r} = 0.921 \quad \mathbf{s} = 0.179 \quad \mathbf{n} = 57 \quad \mathbf{F} = 20.5$$

$$\text{Optimum } (\pi) = 1.15$$

$$\log \text{MIC}_{(M.avium\ 21d)} = -0.870(\pm 0.137) \pi + 0.395(\pm 0.093) \pi^2 + \Sigma I_n + 2.167(\pm 0.074) \quad (8)$$

$$r = 0.932 \quad s = 0.168 \quad n = 52 \quad F = 21.4$$

$$\text{Optimum } (\pi) = 1.10$$

Using the indicator parameters, the biological activity can be predicted, but only within the framework of the selection of the employed substituents in the acyl moiety. Thus, we attempted to find correlations with physical and chemical parameters as well. In the next step we used the local parameters approach¹³. The application to antituberculotics has been published recently¹⁴. We calculated approximately 10 equations for structure–antimycobacterial activity relationships for each strain. Herein, we present only the statistically most significant equations (see Eqs (9)–(16)). The influence of the substituents on the benzyl ring was again expressed with the π constants. The influence of the substituents on the acyl moiety was expressed using hydrophobic constants π with regard to the hydroxy group ($\pi^-_{1\text{OH}}$) and carbonyl group ($\pi_{1\text{CO}}$). In structure–antimycobacterial activity relationships for *M. kansasii* and *M. avium* (21 day incubation), Hammett constant values had to be used. The use of all the above parameters was necessary, as we attempted to find the most active compounds.

$$\log \text{MIC}_{(M.tuber.\ 14d)} = -0.893(\pm 0.135)(\pi^-_{1\text{OH}}) - 0.738(\pm 0.143)(\pi_{1\text{CO}}) - 0.276(\pm 0.053)(\pi_2) + 2.042(\pm 0.048) \quad (9)$$

$$r = 0.797 \quad s = 0.211 \quad n = 56 \quad F = 30.2$$

$$\log \text{MIC}_{(M.tuber.\ 21d)} = -1.001(\pm 0.124)(\pi^-_{1\text{OH}}) - 0.867(\pm 0.129)(\pi_{1\text{CO}}) - 0.205(\pm 0.049)(\pi_2) + 2.099(\pm 0.046) \quad (10)$$

$$r = 0.833 \quad s = 0.180 \quad n = 48 \quad F = 33.4$$

$$\log \text{MIC}_{(M.kans. 14d)} = -0.485(\pm 0.136)(\pi_1)_{\text{CO}} + 0.198(\pm 0.074)(\pi_1)_{\text{CO}}^2 - 0.232(\pm 0.053)(\pi_2) + 2.159(\pm 0.049) \quad (11)$$

$$r = 0.681 \quad s = 0.194 \quad n = 51 \quad F = 13.6$$

$$\text{Optimum } (\pi_1)_{\text{CO}} = 1.22$$

$$\log \text{MIC}_{(M.kans. 21d)} = -0.695(\pm 0.151)(\pi_1)_{\text{CO}} + 0.277(\pm 0.082)(\pi_1)_{\text{CO}}^2 - 0.237(\pm 0.056)(\pi_2) + 2.340(\pm 0.058) \quad (12)$$

$$r = 0.757 \quad s = 0.206 \quad n = 45 \quad F = 18.4$$

$$\text{Optimum } (\pi_1)_{\text{CO}} = 1.25$$

$$\log \text{MIC}_{(M.kans.clin. 14d)} = 0.255(\pm 0.104)(\sigma_1)_{\text{CO}} - 0.2135(\pm 0.050)(\pi_1)_{\text{CO}} - 0.275(\pm 0.049)(\pi_2) + 2.110(\pm 0.0477) \quad (13)$$

$$r = 0.720 \quad s = 0.188 \quad n = 53 \quad F = 17.7$$

$$\log \text{MIC}_{(M.kans.clin. 21d)} = 0.479(\pm 0.118)(\sigma_1)_{\text{CO}} - 0.350(\pm 0.055)(\pi_1)_{\text{CO}} - 0.292(\pm 0.055)(\pi_2) + 2.219(\pm 0.054) \quad (14)$$

$$r = 0.797 \quad s = 0.201 \quad n = 46 \quad F = 24.3$$

$$\log \text{MIC}_{(M.avium 14d)} = 0.728(\pm 0.129)(\sigma_1)_{\text{CO}} - 1.018(\pm 0.148)(\pi_1)_{\text{CO}} + 0.374(\pm 0.084)(\pi_1)_{\text{CO}}^2 - 0.938(\pm 0.174)(\pi_2) + 0.407(\pm 0.117)(\pi_2)^2 + 2.225(\pm 0.060) \quad (15)$$

$$r = 0.847 \quad s = 0.227 \quad n = 57 \quad F = 25.8$$

$$\text{Optimum } (\pi_1)_{\text{CO}} = 1.37$$

$$\text{Optimum } (\pi_2) = 1.15$$

$$\begin{aligned} \log \text{MIC}_{(M.avium\ 21d)} = & 0.704(\pm 0.128)(\sigma_1)_{\text{CO}} - 1.091(\pm 0.143)(\pi_1)_{\text{CO}} + \\ & + 0.374(\pm 0.081)(\pi_1)_{\text{CO}}^2 - 0.798(\pm 0.172)(\pi_2) + \\ & + 0.327(\pm 0.117)(\pi_2)^2 + 2.343(\pm 0.062) \end{aligned} \quad (16)$$

$$r = 0.861 \quad s = 0.216 \quad n = 52 \quad F = 26.4$$

$$\text{Optimum } (\pi_1)_{\text{CO}} = 1.45$$

$$\text{Optimum } (\pi_2) = 1.22$$

From Eqs (9)–(16), in the acyl moiety the lipophilicity seems to be more important. The influence of electronic effects was found only in structure-antimycobacterial activity relationships against *M. kansasii* (clinically isolated strains) and *M. avium*. In all the cases electron-accepting effect expressed by the substituent constants oriented with respect to the carbonyl group decreases the activity. The advantage of this approach is the possibility of general prediction of new structures (compared with the use of indicator variables). The results of this study will be used in the development of new antituberculotics.

In conclusion, *N*-benzylsalicylamides constitute a new group of potential antituberculotics. Their structure-activity relationships varied for different strains.

This work is part of the research projects No. MSM 111600001 of the Ministry of Education, Youth and Sports of the Czech Republic and was supported by the Grant Agency of Czech Republic (grant No. 203/02/0082), the Grant Agency of the Charles University (grant No. 234/2000/Ch/FaF) and by the Higher Education Development Fund (grant No. 2251/2000-G4).

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