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(4-Arylsulfamoyl)phenylcarbamic Acid Esters: I. Synthesis and Activity Against Herpes Viruses

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Abstract—Aiming to modify the biological activity of sulfonamides, a number of alkyl (4-arylsulfamoyl)-phenylcarbamates were prepared in 50–70% yield. Biological screening showed that the target compounds possessed a high activity against herpes viruses as well as a traditional antibiotic one.

Keywords: sulfonamides, phenylcarbamates, carbamic acid, lipophilicity, bioreversible protection, activity against herpes viruses

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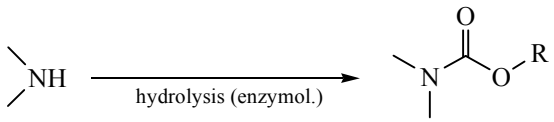
In the last decade sulfonamides, which are one of the oldest classes of antibacterial drugs, have to some extent lost their significance and have very limited indications for use. They are considerably inferior to modern penicillin and cephalosporin antibiotics as well as fluoroquinolones [1]. Nevertheless, the mechanism of biological action of sulfonamides, namely their structural similarity with *para*-amino benzoic acid, an important precursor in the biosynthesis of tetrahydrofolate and tetrahydromethanopterin, makes it possible to expand the application of these drugs.

The accumulation and processing of quantitative information on the structure–activity relationship of sulfonamides in earlier publications led to the conclusion that the presence of a free amino group in the position 4 contributes to the appearance of the biological activity. If the group is substituted, the substance is inactive, except when the substituent is removed by hydrolysis in vivo [2]. Xenobiotics containing a primary amino group are known to be subjected to enzymatic oxidative deamination in the body [3], and, therefore, this group needs to be chemically protected. Most often, for this purpose acylation or introducing of aromatic or heterocyclic moieties are used. In this case the mechanism of biological action of sulfonamides may be considerably changed, as evidenced by numerous examples. In particular, *N*-sulfanyl-5-aminoindolines were found to possess antitumor activity [4]; N^1- and N^4-substituted 3,5-dinitrosulfanylamides showed high antiprotozoal activity [5]. Stranix et al. [6] have found that 2-amino-*N*-{5-[(4-aminobenzenesulfonyl)isobutylamino]-6-hydroxyhexyl}-3-arylpropionamides are inhibitors of HIV protease.

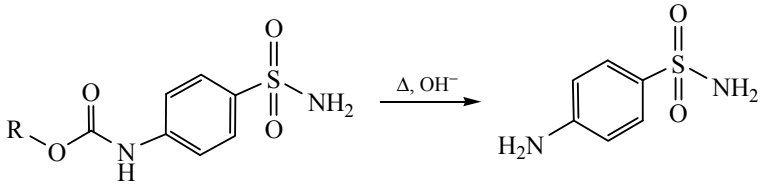


We have suggested [7] that bioreversible modification of the amino group to give alkoxycarbonylamide can improve the efficiency of the physiological action of sulfonamides.

Unlike acylamides, in this case not spontaneous, but enzymatic hydrolysis should occur in vivo. Thus, it shall provide slowing the decay rate of the starting materials and the strengthening of their physiological action. In addition, the compound becomes non-ionizable, which increases its lipophilicity and facilitates the transport through biological membranes. Furthermore, there is the possibility of regulating the hydrophobic properties of the sulfanylamide molecule by altering the hydrocarbon chain length in the alkoxycarbonylamide moiety.

Preliminary experiments demonstrated that non-enzymatic hydrolysis of (4-sulfamoylphenyl)carbamic

Scheme 1.



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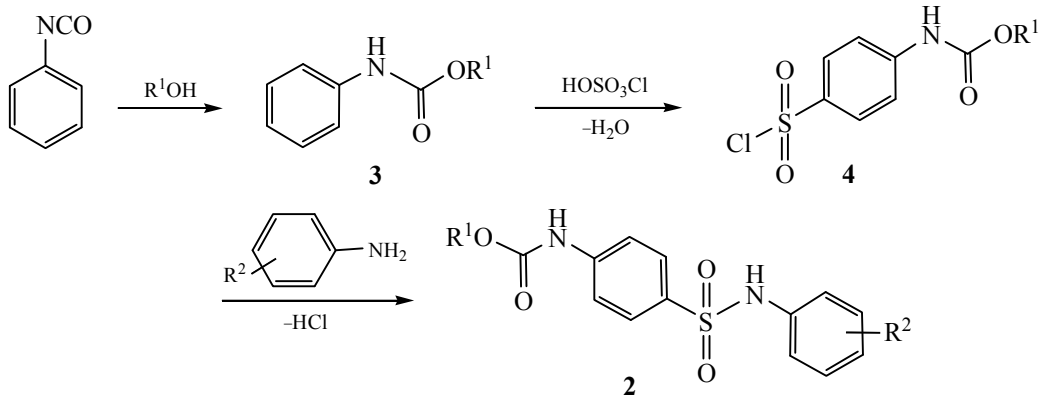
Scheme 2.



2

acid alkyl esters **1** occurred under rigid conditions to give 4-aminobenzenesulfonamide (Scheme 1). The reaction proceeded via boiling a suspension of compounds **1** in aqueous alkali for many hours.

The reaction time increases with the lengthening chain of substituent R. This confirms the assumption of relative stability of alkoxycarbonylamides in vivo. Here we describe the synthesis and biological activity of a number of (4-arylsulfamoyl)phenylcarbaminic acid esters **2a**–**2hh** (Table 1). Synthesis of the target compounds was carried out in accordance with Scheme 2.

Phenylcarbamic acid alkyl esters **3** were prepared by reacting equimolar amounts of phenyl isocyanate and the corresponding alcohol at room temperature. The reaction products obtained in the yields close to quantitative were recrystallized from hexane. Physicochemical characteristics of phenylcarbamates **3** coincided with the published data [8].

Alkyl 4-(chlorosulfonyl)phenylcarbamates **4** prepared by reaction of chlorosulfonic acid with phenylcarbamates **3** were slightly colored crystalline solids (Table 2). For introducing sulfonyl chloride substituent into the position 4 of the aromatic fragment of phenylcarbamate 4–5-fold molar excess of chlorosulfonic acid was required. Reduction of the acid excess resulted in a substantial decrease in the yield of the target compounds **4**.

Structure of chlorides **4** was proved by IR and ^{1}H NMR spectroscopy methods. Thus, their IR spectra were characterized by absorption bands corresponding to the stretching vibrations (2820–2960 cm^{-1}) and bending (1380–1450 cm^{-1}) vibrations of the C–H bonds in alkoxy groups. The ^{1}H NMR spectra contained a multiplet signal at 7.3–7.7 ppm characteristic of the aromatic protons.

The target esters of (4-arylsulfamoyl)phenylcarbamic acid **2a**–**2hh** were prepared by reacting acid chlorides with substituted anilines in the presence of pyridine; the optimum molar ratio **4** : pyridine : substituted aniline = 1.3 : 2 : 1. The failure to comply with the specified ratio led to the contamination of the final reaction products with anilines impurities which are difficult to remove.

Structure of sulfonamides **2a**–**2hh** was confirmed by IR, NMR and UV spectroscopy data. The UV spectra of the resulting compounds contained the absorption band λ_{max} = 245–255 nm with a pronounced shoulder at λ_{max} = 275–280 nm due to the presence of two aromatic rings in the molecules.

In the IR spectra of the substituted amides **2** there were characteristic absorption bands in the ranges of

Table 1. Yields, melting points, R_f values, and elemental analysis data for (4-arylsulfamoyl)phenylcarbamates **2a–2hh**

Comp. no.	R^1	R^2	Yield, %	mp, °C	R_f[a]	Found, %			Formula	Calculated, %		
						C	H	N		C	H	N
2a	Me	2-MeC_6H_4	87	207	0.57	55.9	4.99	8.70	$C_{15}H_{16}N_2O_4S$	56.2	5.03	8.74
2b	Bu	4-BrC_6H_4	79	185	0.39	47.4	4.35	6.72	$C_{17}H_{19}BrN_2O_4S$	47.8	4.48	6.56
2c	Bu	4-$NO_2C_6H_4$	77	189	0.41	52.1	4.65	10.5	$C_{17}H_{19}N_3O_6S$	51.9	4.87	10.7
2d	Bu	2-MeC_6H_4	82	136	0.38	59.4	6.31	7.58	$C_{18}H_{22}N_2O_4S$	59.6	6.12	7.73
2e	Bu	2-ClC_6H_4	77	138	0.40	53.7	5.05	7.61	$C_{17}H_{19}ClN_2O_4S$	53.3	5.00	7.32
2f	Bu	3-BrC_6H_4	80	158	0.28	48.0	4.60	6.25	$C_{17}H_{19}BrN_2O_4S$	47.8	4.48	6.56
2g	Bu	Ph	79	149	0.29	58.3	5.92	7.89	$C_{17}H_{20}N_2O_4S$	58.6	5.79	8.04
2h	Bu	2,5-$Me_2C_6H_3$	89	151	0.30	60.9	6.15	7.33	$C_{19}H_{24}N_2O_4S$	60.6	6.43	7.44
2i	Bu	4-FC_6H_4	85	145	0.34	55.5	5.43	7.77	$C_{17}H_{19}FN_2O_4S$	55.7	5.23	7.65
2j	C_5H_{11}	2,6-$Cl_2C_6H_3$	70	125	0.38	50.2	4.64	6.40	$C_{18}H_{20}Cl_2N_2O_4S$	50.1	4.67	6.49
2k	C_5H_{11}	4-BrC_6H_4	75	137	0.29	48.8	4.93	6.51	$C_{18}H_{21}BrN_2O_4S$	49.0	4.80	6.35
2l	C_5H_{11}	2-MeC_6H_4	91	143	0.29	60.3	6.59	7.28	$C_{19}H_{24}N_2O_4S$	60.6	6.43	7.44
2m	C_5H_{11}	2-ClC_6H_4	67	149	0.35	54.9	5.62	6.95	$C_{18}H_{21}ClN_2O_4S$	54.5	5.33	7.06
2n	C_5H_{11}	2-IC_6H_4	79	134	0.38	44.2	4.288	5.80	$C_{18}H_{21}IN_2O_4S$	44.3	4.33	5.74
2o	C_5H_{11}	3-BrC_6H_4	85	160	0.40	48.7	4.51	6.49	$C_{18}H_{21}BrN_2O_4S$	49.0	4.80	6.35
2p	C_5H_{11}	Ph	70	153	0.30	60.0	5.93	7.91	$C_{18}H_{22}N_2O_4S$	59.6	6.12	7.73
2q	C_5H_{11}	2,5-$Me_2C_6H_3$	93	162	0.31	61.4	6.79	7.12	$C_{20}H_{26}N_2O_4S$	61.5	6.71	7.17
2r	C_5H_{11}	4-FC_6H_4	76	143	0.32	56.5	5.81	7.29	$C_{18}H_{21}FN_2O_4S$	56.8	5.57	7.36
2s	C_6H_{13}	4-BrC_6H_4	84	149	0.20	49.9	5.17	6.37	$C_{19}H_{23}BrN_2O_4S$	50.1	5.09	6.15
2t	C_6H_{13}	2-MeC_6H_4	87	146	0.19	61.7	6.50	7.32	$C_{20}H_{26}N_2O_4S$	61.5	6.71	7.17

Table 1. (Contd.)

Comp. no.	R^1	R^2	Yield, %	mp, °C	R_f[a]	Found, %			Formula	Calculated, %		
						C	H	N		C	H	N
2u	C_6H_{13}	2-ClC_6H_4	79	143	0.31	55.5	5.55	6.79	$C_{19}H_{23}ClN_2O_4S$	55.5	5.64	6.82
2v	C_6H_{13}	2,5–$Me_2C_6H_3$	91	142	0.33	62.2	6.85	6.89	$C_{21}H_{28}N_2O_4S$	62.4	6.98	6.92
2w	C_6H_{13}	Ph	87	127	0.36	60.3	6.12	7.61	$C_{19}H_{24}N_2O_4S$	60.6	6.43	7.44
2x	C_7H_{15}	4-BrC_6H_4	75	145	0.14	50.9	5.27	6.01	$C_{20}H_{25}BrN_2O_4S$	51.2	5.37	5.97
2y	C_7H_{15}	2-ClC_6H_4	71	144	0.25	55.9	5.87	6.57	$C_{20}H_{25}ClN_2O_4S$	56.5	5.93	6.59
2z	C_7H_{15}	2,6-$Cl_2C_6H_3$	77	147	0.31	51.9	5.20	6.10	$C_{20}H_{24}Cl_2N_2O_4S$	52.3	5.27	6.10
2aa	Me	4-BrC_6H_4	70	260 (decomp.)	0.60	43.6	3.40	7.30	$C_{14}H_{13}BrN_2O_4S$	43.6	3.37	7.27
2bb	Et	4-BrC_6H_4	75	232	0.49	45.0	3.74	7.00	$C_{15}H_{15}BrN_2O_4S$	45.1	3.79	7.02
2cc	Bu	2-IC_6H_4	65	111	0.30	43.3	3.97	6.11	$C_{17}H_{19}IN_2O_4S$	43.0	4.04	5.91
2dd	Bu	3-C(O)MeC_6H_4	90	121	0.73[b]	59.2	6.00	7.06	$C_{19}H_{22}N_2O_5S$	58.4	5.68	7.17
2ee	Bu	2-OMe-4-$NO_2C_6H_3$	78	161	0.65[b]	51.5	4.81	9.81	$C_{18}H_{21}N_3O_7S$	51.1	5.00	9.92
2ff	Bu	2,6-$Cl_2C_6H_3$	77	149	0.34[c]	48.7	4.40	6.72	$C_{17}H_{18}Cl_2N_2O_4S$	48.9	4.35	6.71
2gg	Bu	2,3-$Cl_2C_6H_3$	70	129	0.49[d]	48.5	4.58	6.66	$C_{17}H_{18}Cl_2N_2O_4S$	48.9	4.35	6.71
2hh	Bu	3-OHC_6H_4	25	157	0.55	55.4	5.77	7.94	$C_{17}H_{20}N_2O_5S$	56.0	5.53	7.69

[a] Chloroform–methanol, 3 : 1. [b] Acetone–hexane, 1 : 1. [c] Carbon tetrachloride–isopropanol, 9 : 1. [d] Acetone–hexane, 1 : 2.

Table 2. Yields, melting points and elemental analysis data for (4-achlorosulfonylphenyl)carbamates **4a–4g**

Comp. no.	R^1	Yield, %	Mp, °C	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
4a	Me	60	87	39.1	3.15	5.70	$C_8H_8ClNO_4S$	38.5	3.23	5.61
4b	Et	71	42	39.9	3.87	5.43	$C_9H_{10}ClNO_4S$	41.0	3.82	5.31
4c	Pr	77	55	43.1	4.41	4.99	$C_{10}H_{12}ClNO_4S$	43.2	4.36	5.04
4d	Bu	75	65	45.4	4.73	4.90	$C_{11}H_{14}ClNO_4S$	45.3	4.84	4.80
4e	C_5H_{11}	68	77	46.9	5.17	4.75	$C_{12}H_{16}ClNO_4S$	47.1	5.27	4.58
4f	C_6H_{13}	63	92	48.4	5.80	4.82	$C_{13}H_{18}ClNO_4S$	48.8	5.67	4.38
4g	C_7H_{15}	79	109	50.5	6.10	4.34	$C_{14}H_{20}ClNO_4S$	50.4	6.04	4.20

Table 3. ^{1}H NMR spectral data for (4-arylsulfamoyl)phenylcarbamates **2a–2hh**

Comp. no.	δ, ppm			Comp. no.	δ, ppm		
	OCH_2[a]	NH(Ar)	NH(S)		OCH_2	NH(Ar)	NH(S)
2a	3.66[б]	9.40	10.1	**2r**	4.10	10.08	10.10
2b	4.10	**2**0.2	10.35	**2s**	4.05	10.1	10.4
2c	4.10	**2**0.2	11.15	**2t**	4.10	9.40	10.1
2d	4.15	9.42	10.1	**2u**	4.12	9.82	10.1
2e	4.10	9.80	10.1	**2v**	4.10	9.40	10.1
2f	4.11	**2**0.2	10.45	**2w**	4.10	10.08	10.13
2g	4.10	**2**0.06	10.12	**2x**	4.10	10.1	10.3
2h	4.11	9.30	10.08	**2y**	4.11	9.80	10.1
2i	4.10	**2**0.08	10.1	**2z**	4.10	9.40	10.1
2j	4.12	9.95	10.1	**2aa**	3.65[b]	10.1	10.3
2k	4.05	**2**0.05	10.3	**2bb**	4.12	10.1	10.4
2l	4.10	9.4	10.1	**2cc**	4.09	9.80	10.1
2m	4.10	9.83	10.1	**2dd**	4.12	10.5	10.9
2n	4.12	9.50	10.1	**2ee**	4.10	9.50	10.7
2o	4.10	**2**0.2	10.35	**2ff**	4.11	10.1	10.6
2p	4.10	**2**0.05	10.12	**2gg**	4.10	9.50	10.8
2q	4.10	9.4	10.1	**2hh**	4.11	10.1	10.7

[a] The signals of methylene protons appeared as characteristic triplets with spin-spin coupling constant J = 6.4 Hz. [b] OMe.

1750–1690 cm^{-1} [NHC(O)O], 1370–1333 and 1178–1159 cm^{-1} (O=S=O). Furthermore, the absorption at 3390–3260 cm^{-1} corresponded to the stretching vibrations of NH group. The absorption in the ranges of 1600–1500 and 850 cm^{-1} was due to the stretching vibrations of the aromatic ring.

The ^{1}H NMR data for amides **2a–2hh** are listed in Table 3.

The biological screening showed that the target compounds, except for **2aa**, **2bb,** and **2cc**, exhibit antibacterial activity (*Mycobacterium smegmatis*); in

vitro minimum inhibitory concentration values MIC_{100} were in the range of 6.2–25 μg mL. Compounds **2a**–**2z** and **2dd–2hh** showed a high activity against herpes virus type 1 and 2. In particular, amide **2j** possessed reliable virus inhibiting activity towards in vivo model herpes pneumonia and was superior to Acyclovir at the same dose (titer of virus $lgCTD_{50}$ in the lungs of mice for 3 days after infection for the reference compound, **2j,** and Acyclovir was 3.6±0.15, 1.0±0.11 and 1.4±0.34, respectively). It was interesting to note that compounds **2a**, **2b**, **2d–2i**, **2k–2m**, **2o–2v**, and **2aa** moderately inhibited the strain of vesicular stomatitis virus (*Stomatitis vesicularis*).

In summary, about a third of compounds obtained are inducers of endogenous interferon, which confirms desirability of searching for new antiviral drugs in a series of substituted sulfonamides.

EXPERIMENTAL

^{1}H NMR spectra of the solutions in DMSO-d_6 were recorded on a Bruker WM-400 spectrometer (400.13 MHz) using the residual proton signals of DMSO as internal reference. Individuality of the compounds obtained was monitored by HPLC (column Luna C-18 4.6 × 250 mm, mobile phase: 0.1% solution of trifluoroacetic acid in water (A), water–acetonitrile, 70 : 30 (B); flow rate 1.5 mL/min). Elemental analysis was performed on analyzers Hewlett Packard B-185 and Leco CHNS-932. IR spectra were registered on a FSM-1201 (KBr) and SHIMADZU FTIR-8400S spectrometers. UV spectra were recorded on a 1700 PharmaSpec 230VCE UV spectrophotometer.

Organic solvents and starting materials were purified according to the known methods [9].

Antiviral and antimycobacterial activity of the target compounds was studied in relation to the standard strains from the collection of the Department of Microbiology of the Pavlov St. Petersburg First State Medical University as described in [10].

Pentyl phenylcarbamate (3e). Pentan-1-ol (88 g) was added dropwise with stirring to phenyl isocyanate (119 g). The reaction mixture was stirred until crystallization. Next, the mixture was allowed to stand overnight at room temperature. The resulting product was recrystallized from hexane and dried at 60°C. Yield 190 g (92%).

Phenylcarbamic acid esters **3a**–**3g** were prepared similarly.

Pentyl (4-chlorosulfonylphenyl)carbamate (4e). Phenylcarbamic acid pentyl ester (20.7 g) was added by portions with stirring to chlorosulfonic acid (50 g) at 30–35°C. Then the reaction was slowly warmed to 50°C and kept at this temperature for 2 h. Next, the reaction mixture was slowly poured into ice water with vigorous stirring, while maintaining the reaction mixture temperature no higher than 20°C. The resulting precipitate was filtered off, washed with cold water until the neutral filtrate (pH 7), and dried at 60°C. Yield 20.8 g (68%).

(4-Chlorosulfonylphenyl)carbamic acid esters **4a**–**4e** were prepared similarly.

Pentyl [4-(2,6-dichlorophenylsulfamoyl)-4-phenyl]-carbamate (2j). To a mixture of 1.6 g of 2,6-dichloroaniline and 1.6 g of pyridine heated to 85°C was added in small portions at stirring 4 g of pentyl (4-chlorosulfonylphenyl)carbamate **4e**. The reaction mixture was stirred for 1 h at 80°C, and then diluted (1 : 1) with warm water (40°C). pH of the reaction mixture was adjusted to 3.4 with hydrochloric acid. After cooling to room temperature the resulting precipitate was filtered off, washed with water, recrystallized from 80% ethanol, and dried at 80°C. Yield 3 g (70%).

(4-Arylsulfamoyl-4-phenyl)carbamic acid esters **2a–2hh** were prepared analogously. Physicochemical characteristics of the target compounds are given in Tables 1 and 3.

Pentyl (4-sulfamoylphenyl)carbamate (1). Compound **4e** (3.06 g) was added in small portions to 50 mL of 25% aqueous ammonia with stirring, while maintaining the reaction mixture temperature below 30°C. The mixture was then heated for 1 h at 60°C and pH 9.5. After cooling to room temperature the resulting precipitate was filtered off, washed with water, and dried at room temperature. Yield 2.75 g (96%).

Hydrolysis of pentyl (4-sulfamoylphenyl) carbamate. A suspension of (4-sulfamoylphenyl) carbamic acid pentyl ester **1** in 30% sodium hydroxide was stirred until complete dissolution. The reaction mixture was heated on a boiling water bath. The reaction progress was monitored by TLC. The hydrolysis of compound **1** was completed in 4 h.

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