ORIGINAL ARTICLE

NEW SYNTHESIS IN THE N-[4-[(PHENYLCARBAMOYL)AMINO]-PHENYL]BENZENESULFONAMIDE DERIVATIVES SERIES. NOTE 1

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Abstract

A series of N-[4-[(phenylcarbamoyl)amino]phenyl]benzenesulfonamide derivatives was prepared by Curtius degradation of corresponding azide, followed by condensation with primary aromatic amines. Such compounds may have different pharmacological properties, such as antibacterial, antifungal, hypoglicemic, diuretic. The structures of these substances were confirmed by elemental analysis, IR and NMR – spectrometry.

Rezumat

O serie de derivați ai N-[4-[(fenilcarbamoil)amino]fenil]benzensulfonamidei a fost preparată prin degradarea Curtius a azidei corespunzătoare, urmată de condensarea cu diferite amine aromatice primare; aceştia pot avea diverse proprietăți farmacologice, precum acțiunea antibacteriană, antifungică, hipoglicemiantă sau diuretică. Structurile acestor substanțe au fost confirmate cu ajutorul analizei elementale şi spectrometriei în IR şi RMN.

Keywords: benzenesulfonamide, urea-derivatives, Curtius degradation, halogenated compounds

Introduction

Sulfonamides are known since 1932, when the company IG Farben registered a patent in which they described the obtaining process of a compound that has a sulfonamide moiety [7]. The antibacterial and hypoglycaemic actions have been associated to this structure for the first time [3]. They are clinically used as antimicrobial medicines, because they have the capacity to prevent the synthesis of folic acid, inhibiting the dihydropteroate synthase [2, 8]. An important class of derivatives is used for their diuretic and antihypertensive properties [9], and also as antiglaucoma agents [6].

In recent studies, new pharmacological properties were researched and assigned for derivatives of sulfonamides: inhibition of matrix metalloproteinases (involved in chronic obstructive pulmonary disease, ulcer, asthma and cancer) [5], antidepressant effect (more active than imipramine for some compounds) [10], inhibition of fibrillogenesis and oligomer formation, free radical scavenging and modulation of cholinesterase activity (properties that can be used in the treatment of Alzheimer's disease) [1].

Another important aspect that was studied regarding the pharmacology of sulfonamides derivatives was the effect on carbonic anhydrases. These are ubiquitous metalloenzymes, expressed in both prokaryotes and eukaryotes. They are involved in a long series of physiological processes, catalysing the reversible hydration of carbon dioxide with the production of bicarbonate and protons. Processes like tumorigenicity, ureagenesis, lipogenesis and gluconeogenesis can be influenced [12, 13] by inhibiting these enzymes.

This article underlines a new method for obtaining original sulfonamides derivatives having halogenated radicals, using as a starting point an azide. The substances may have various pharmacological properties.

Materials and Methods

Melting points were measured in open capillary tubes on an Electrothermal 9100 apparatus and are uncorrected.

The Fourier-transform infrared (FT-IR) spectra of the all synthesized compounds were performed on a Bruker Vertex 70 FT-IR spectrometer (Bruker Corporation, Billerica, MA, USA). The spectra were acquired with 32 scans over a range of 400 to 4000 cm^{-1}. The spectral resolution was 4 cm^{-1}.

The signal intensities (height) were denoted by the following abbreviations: w = weak, m = medium, s = strong, v = variable. The NMR spectra were recorded using a Gemini 300BB instrument at room

temperature, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C or Bruker Avance III 500 MHz. The chemical shifts were recorded in δ units (ppm), relative to residual peak of the deuterated solvent (DMSO-d6). Tetramethylsilane was used as internal standard. The coupling constants values are reported in Hertz and the splitting patterns are abbreviated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad; dd, double doublet; td, triple doublet; tt, triple triplet. The elemental analysis was performed on a Perkin Elmer CHNS/O Analyser Series II 2400 apparatus and the results were in agreement with the calculated values.

All starting materials and solvents were purchased from commercial suppliers and used without purification, unless otherwise noted.

Intermediate synthesis

In order to obtain new compounds, we wanted to introduce an urea group in the structure of the phenylsulfonamides. Urea and its derivatives are known for their biological effects including anti-bacterial, antiviral, anticonvulsant, antiprotozoal, anti-inflammatory, antidepressant, antiulcer, anti-acethylcholinesterase, antiatherosclerotic, hypo-glycaemic, and antitumour activities [14]. For these reasons we decided to combine the two moieties, in order to obtain a new molecule with a better pharmacological profile.

The main compound used in the new synthesis was 4-(benzensulfonamido)benzoyl azide (VI) which was obtained using an original adaptation from literature data [4, 11], following the general route of synthesis, presented in Figure 1.

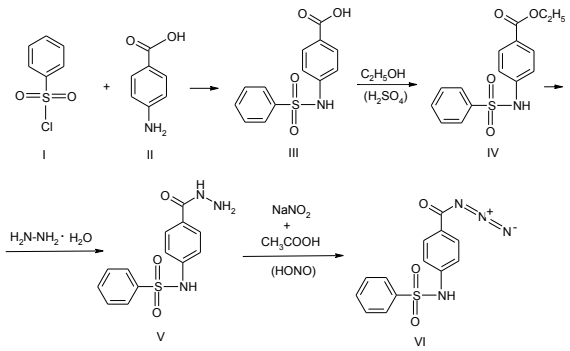


Figure 1.
The synthesis of the main intermediate compound (VI)

For the synthesis of 4-[(phenylsulfonyl)amino]-benzoic acid (III), benzensulfochlorine (I) and 4-aminobenzoic acid (II) were condensed. 25 g of 4-aminobenzoic acid were dissolved in a solution of potassium carbonate 8%, and 35 mL of benzen-sulfochlorine were dropwise added. After half an hour, the mixture was boiled for 10 - 15 minutes, cooled and acidulated with concentrated HCl. The precipitate was filtered and purified by dissolution in 10% NaOH solution and precipitated again in concentrated HCl (80% yield; m.p. 204°C (water)).

The acid (III) was transformed in the ester (IV), which gave the hydrazide (V) by condensing with hydrazine hydrate.

In a round bottom flask equipped with a vertical condenser were added 2.77 g (0.01 mole) of 4-[(phenylsulfonyl)amino]benzoic acid (III) and 33 mL (0.553 mole) of absolute ethanol. We added 1.22 mL of sulfuric acid (0.023 mole) were and the mixture was refluxed for 3 hours. The flask was cooled and the compound was precipitated using a solution of sodium carbonate. We obtained 2.83 g of white precipitate (92.7% yield; m.p. 184 - 185°C (ethanol)).

In a round bottom flask the ester obtained in the previous phase (1.22 g – 0.004 mole) was dissolved in absolute ethanol, and 8 mL (0.1646 mole) of hydrazine hydrate were added. The mixture was refluxed for 4 hours. We obtained a precipitate (0.788 g) which was recrystallized from ethanol (67.93% yield; m.p. 231 - 232°C).

This hydrazide was transformed in the azide (VI) by a diazotation reaction. We used 0.584 g (0.002 mole) of hydrazide dissolved in 10 mL glacial acetic acid. When the solution temperature was 5 - 8°C, we added 4 mL of sodium nitrate solution (4% solution) (freezing at 0°C) using a dropping funnel. After adding chopped ice to the reaction mixture and keeping the flask at room temperature for about an hour, the white-yellow precipitate was filtered and washed with cold water, resulting 0.546 g of azide (VI) (90.1% yield; m.p. 141 - 142°C).

Final compound synthesis (VII- XV)

The new derivatives of N-[4-[(phenylcarbamoyl)-amino]phenyl]benzenesulfonamide were obtained treating the previously obtained azide with halogen substituted aromatic amines in dioxane, following the general procedure described in Figure 2.

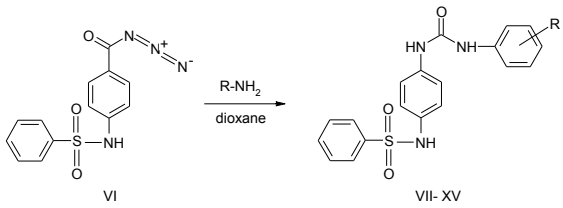


Figure 2.
Synthesis of new derivatives of N-[4-[(phenyl-carbamoyl)amino]phenyl]benzenesulfonamide (VII - XV)

We dissolved 0.00074 mole of azide VI in 15 mL dioxane. The solution was added gradually in a warm two neck round bottom flask using a dropping funnel. The solution was refluxed for about an hour (following the Curtius degradation of azide resulting the isocyanate) and we added the equimolecular

quantities of amine dissolved in 5mL dioxane using the same dropping funnel. We continued the heating under reflux for about another hour. After concentration at *vacuum*, the crude compound was recrystallized from ethanol.

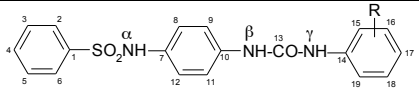
Results and Discussion

Using this general method, we obtained nine new derivatives of N-[4-[(phenylcarbamoyl)amino]phenyl]-benzenesulfonamide having a halogen aromatic moieties. The compounds are solid, white, yellow or light violet microcrystals, having acicular or prismatic crystals. The structures were confirmed by elemental analysis, IR and NMR spectra.

The structures of the new compounds, molecular formula, molecular mass, melting points, and yields are presented in Table I (the carbon atoms numbering was done in close correlation with the signals attribution of nuclear magnetic resonance spectra, as it is described below).

Table I

Characterization data of the new compounds



No.	R	Molecular formula	Molecular mass	m.p. (^{0}C)	Yield (%)
VII	*ortho* -Cl	$C_{19}H_{16}N_3ClO_3S$	401.865	196 – 197	78.18
VIII	*meta* -Cl	$C_{19}H_{16}N_3ClO_3S$	401.865	185 – 186	78.18
IX	*para* -Cl	$C_{19}H_{16}N_3ClO_3S$	401.865	224 – 225	54.38
X	*ortho* -Br	$C_{19}H_{16}N_3BrO_3S$	446.324	197 – 198	52.03
XI	*meta* -Br	$C_{19}H_{16}N_3BrO_3S$	446.324	195 – 196	51.11
XII	*para* -Br	$C_{19}H_{16}N_3BrO_3S$	446.324	228 – 229	64.27
XIII	*ortho* -I	$C_{19}H_{16}N_3IO_3S$	493.318	203 – 204	69.22
XIV	*meta* -I	$C_{19}H_{16}N_3IO_3S$	493.318	205 – 206	66.45
XV	*para* -I	$C_{19}H_{16}N_3IO_3S$	493.318	232 – 233	49.84

In the following are presented the results of elemental and ^{1}H and ^{13}C magnetic resonance analysis for the compounds VII - XV.

Compound VII: *N-[4-[(2-chlorophenylcarbamoyl)-amino]phenyl]benzenesulfonamide*

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 10.05 (bs, 1H, H-α, deuterable); 9.34 (s, 1H, HN, H-β, deuterable); 8.26 (s, 1H, HN, H-γ, deuterable); 8.12 (dd, 1H, H-19, 1.7, 8.1); 7.71 (dd, 2H, H-2, H-6, 0.8, 8.6); 7.60 (tt, 1H, H-4, 0.8, 8.6); 7.53 (t, 2H, H-3, H-5, 8.6); 7.44 (dd, 1H, H-16, 1.7, 8.1); 7.31 (d, 2H, H-9, H-11, 8.6); 7.28 (td, 1H, H-17, 8.1, 1.7); 7.01 (td, 1H, H-18, 8.1, 1.7); 7.00 (d, 2H, H-8, H-12, 8.6).

^{13}C-NMR (dmso-d6, δ ppm): 152.06 (C-13); 139.48 (C-1); 136.28 (C-7); 131.66 (C-10); 135.92 (C-14); 121.87 (C-15); 132.78 (C-4); 129.18 (C-3, C-5); 126.68 (C-2, C-6); 122.12 (C-8, C-12); 118.85 (C-9, C-11); 129.20 (C-16); 127.58 (C-17); 123.28 (C-18); 121.25 (C-19).

FT-IR (solid in ATR, ν cm^{-1}): 3360s; 3334m; 3167w; 3068w; 1689vs; 1592s; 1537s; 1506s; 1469m; 1436m; 1409m; 1389m; 1319m; 1301m; 1213m; 1155vs; 1091m; 1062w; 1036w; 916w; 740m; 729m; 683w; 594m.

Elemental analysis: Calculated: C 56.78%, H 4.013%, N 10.45%, S 7.98%; Found: C 56.65%, H 4.12%, N 10.25%, S 7.81%.

Compound VIII: *N-[4-[(3-chlorophenylcarbamoyl)-amino]phenyl]benzenesulfonamide*

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 10.03 (bs, 1H, H-α, deuterable); 8.83 (s, 1H, HN, H-γ, deuterable); 8.67 (s, 1H, HN, H-β, deuterable); 7.71 (dd, 2H, H-2, H-6, 0.8, 8.6); 7.60 (tt, 1H, H-4, 0.8, 8.6); 7.53 (t, 2H, H-3, H-5, 8.6); 7.28 (d, 2H, H-9, H-11, 8.6); 6.97 (d, 2H, H-8, H-12, 8.6); 7.67 (t, 1H, H-15, 1.1); 7.28 (t, 1H, H-18, 7.8); 7.22 (dd, 1H, H-19, 1.9, 7.8); 6.99 (dd, 1H, H-17, 1.9, 7.8).

^{13}C-NMR (dmso-d6, δ ppm): 152.32 (C-13); 141.25 (C-14); 139.47 (C-1); 136.24 (C-7); 133.17 (C-16); 131.63 (C-10); 132.78 (C-4); 129.18 (C-3, C-5); 126.68 (C-2, C-6); 122.03 (C-8, C-12); 119.15 (C-9, C-11); 130.39 (C-18); 121.41 (C-17); 117.49 (C-15); 116.59 (C-19).

FT-IR (solid in ATR, ν cm^{-1}): 3391m; 3352m; 3114m; 1690vs; 1595vs; 1552s; 1520s; 1484m; 1446w; 1402m; 1321s; 1302m; 1236w; 1212m; 1153vs; 1088m; 917m; 854w; 751w; 728w; 712w; 676m; 646w.

Elemental analysis: Calculated: C 56.78%, H 4.013%, N 10.45%, S 7.98%; Found C 56.55%, H 4.01%, N 10.20%, S 7.89%.

Compound IX: *N-[4-[(4-chlorophenylcarbamoyl)-amino]phenyl]benzenesulfonamide*

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 10.02 (bs, 1H, H-α, HN-SO_2, deuterable); 8.75 (s, 1H, H-γ, deuterable); 8.61 (s, 1H, H-β, deuterable); 7.71 (dd, 2H, H-2, H-6, 0.8, 8.6); 7.60 (tt, 1H, H-4, 0.8, 8.6); 7.53 (t, 2H, H-3, H-5, 8.6); 7.44 (d, 2H, H-16, H-18, 8.7); 7.30 (d, 2H, H-15, H-19, 8.6); 7.29 (d, 2H, H-9, H-11, 8.8); 6.98 (d, 2H, H-8, H-12, 8.8).

The attribution of NH protons was made after the Heteronuclear Multiple Bond Correlation (HMBC) spectra. It is noted a long- range coupling of H-γ with $H^{15,19}$ protons from the para-chlorophenyl

aromatic nucleus. Also there is a long- range coupling of H-β with $H^{9,11}$ protons from the 4-phenyldiamino aromatic nucleus.

From the long distance correlation spectra of HMBC it can be noted that $H^{3,5}$ show a strong HMBC correlations with C^1, and other HMBC couplings are: $H^{9,11}$ - C^7, $H^{8,12}$ - C^{10}, $H^{16,18}$ - C^{14}, and $H^{15,19}$ - C^{17}, which are in agreement with the proposed assignments.

^{13}C-NMR (dmso-d6, δ ppm): 152.42 (C-13); 139.52 (C-1); 138.71 (C-14); 136.42 (C-7); 132.78 (C-4); 131.55 (C-10); 125.36 (C-17); 129.19 (C-3, C-5); 128.66 (C-15, C-19); 126.72 (C-2, C-6); 122.12 (C-8, C-12); 119.73 (C-16, C-18); 119.10 (C-9, C-11).

FT-IR (solid in ATR, ν cm^{-1}): 3314m; 3236s; 3152w; 1651s; 1592m;1545vs; 1508s; 1490m; 1447w; 1433w; 1397m; 1333m; 1307w; 1281w; 1238w; 1218m; 1162s; 1089m; 905w; 825w; 752w; 731m; 685w.

Elemental analysis: Calculated: C 56.78%, H 4.013%, N 10.45%, S 7.98%; Found C 56.89%, H 3.89%, N 10.33%, S 8.1%.

Compound X: *N-[4-[(2-bromophenylcarbamoyl)-amino]phenyl]benzenesulfonamide*

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 10.05 (bs, 1H, H-α, deuterable); 9.39 (s, 1H, HN, H-γ, deuterable); 8.08 (s, 1H, HN, H-β, deuterable); 7.71 (dd, 2H, H-2, H-6, 0.8, 8.6); 7.60 (tt, 1H, H-4, 0.8, 8.6); 7.53 (t, 2H, H-3, H-5, 8.6); 7.28 (d, 2H, H-9, H-11, 8.6); 6.97 (d, 2H, H-8, H-12, 8.6); 8.02 (dd, 1H, H-16, 1.7, 8.2); 7.59 (dd, 1H, H-19, 1.7, 8.2); 7.64 (td, 1H, H-17, 8.2, 1.7); 6.96 (td, 1H, H-18, 8.2, 1.7).

^{13}C-NMR (dmso-d6, δ ppm): 152.12 (C-13); 139.46 (C-1); 137.03 (C-14); 136.35 (C-7); 131.63 (C-10); 113.03 (C-15); 132.80 (C-4); 132.49 (C-19); 129.20 (C-3, C-5); 128.09 (C-17); 126.69 (C-2, C-6); 124.08 (C-18); 122.20 (C-16); 122.12 (C-8, C-12); 118.89 (C-9, C-11).

FT-IR (solid in ATR, ν cm^{-1}): 3304m; 3217vs; 3069w; 1662s; 1601w; 1578m; 1542s; 1507s; 1433m; 1391m; 1335m; 1283m; 1215m; 1155s; 1090m; 1021m; 912m; 790w; 744m; 730m; 717m; 680m; 647m.

Elemental analysis: Calculated: C 51.12%, H 3.613%, N 9.41%, S 7.18%; Found C 51.30%, H 3.5%, N 9.54%, S 7.4%.

Compound XI: *N-[4-[(3-bromophenylcarbamoyl)-amino]phenyl]benzenesulfonamide*

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 10.04 (bs, 1H, H-α, deuterable); 8.82 (s, 1H, HN, H-γ, deuterable); 8.66 (s, 1H, HN, H-β, deuterable); 7.71 (dd, 2H, H-2, H-6, 0.8, 8.6); 7.60 (tt, 1H, H-4, 0.8, 8.6); 7.53 (t, 2H, H-3, H-5, 8.6); 7.28 (d, 2H, H-9, H-11, 8.6); 6.97 (d, 2H, H-8, H-12, 8.6); 7.82 (t, 1H, H-15, 1.3); 7.26 (dd, 1H, H-19, 1.3, 7.7); 7.21 (t, 1H, H-18, 7.7); 7.12 (dd, 1H, H-17, 1.3, 7.7).

^{13}C-NMR (dmso-d6, δ ppm): 152.31 (C-13); 141.38 (C-1); 139.48 (C-14); 136.23 (C-7); 131.64 (C-10); 121.62 (C-16); 132.78 (C-4); 129.18 (C-3, C-5); 126.68 (C-2, C-6); 122.03 (C-8, C-12); 119.17 (C-9, C-11); 130.71 (C-18); 124.33 (C-17); 120.36 (C-15); 117.00 (C-19).

FT-IR (solid in ATR, ν cm^{-1}): 3344m; 3254m; 3142m; 3094m; 1642m; 1607s; 1578m; 1551vs; 1507vs; 1476s; 1435m; 1396m; 1321m; 1301m; 1284m; 1215m; 1154vs; 1087m; 897w; 853w; 827w; 766w; 728m; 675m; 650m.

Elemental analysis: Calculated: C 51.12%, H 3.613%, N 9.41%, S 7.18%; Found C 51.01%, H 3.48%, N 9.62%, S 6.97%.

Compound XII: *N-[4-[(4-bromophenylcarbamoyl)-amino]phenyl]benzenesulfonamide*

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 10.02 (bs, 1H, H-α, deuterable); 8.76 (s, 1H, HN, H-γ, deuterable); 8.62 (s, 1H, HN, H-β, deuterable); 7.71 (dd, 2H, H-2, H-6, 0.8, 8.6); 7.60 (tt, 1H, H-4, 0.8, 8.6); 7.53 (t, 2H, H-3, H-5, 8.6); 7.40 (m, 4H, H-15-16-18-19, syst. AA'BB', 9.1); 7.28 (d, 2H, H-9, H-11, 8.6); 6.97 (d, 2H, H-8, H-12, 8.6).

^{13}C-NMR (dmso-d6, δ ppm): 152.35 (C-13); 139.47 (C-14); 139.12 (C-1); 136.36 (C-7); 131.53 (C-10); 113.19 (C-17); 132.80 (C-4); 131.53 (C-16, C-18); 129.20 (C-3, C-5); 126.69 (C-2, C-6); 122.08 (C-8, C-12); 120.10 (C-15, C-19); 119.02 (C-9, C-11).

FT-IR (solid in ATR, ν cm^{-1}): 3312m; 3236s; 3072w; 1650s; 1601w; 1587m; 1543vs; 1506s; 1486m; 1447w; 1392m; 1332m; 1306w; 1279w; 1216m; 1161s; 1089m; 1069w; 904w; 821w; 752w; 731m; 685w; 637m; 615m.

Elemental analysis: Calculated: C 51.12%, H 3.613%, N 9.41%, S 7.18%; Found C 51.03%, H 3.71%, N 9.65%, S 7.35%.

Compound XIII: *N-[4-[(2-iodophenylcarbamoyl)-amino]phenyl]benzenesulfonamide*

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 10.02 (bs, 1H, H-α, deuterable); 9.34 (s, 1H, HN, H-γ, deuterable); 7.82 (s, 1H, HN, H-β, deuterable); 7.71 (dd, 2H, H-2, H-6, 0.8, 8.6); 7.60 (tt, 1H, H-4, 0.8, 8.6); 7.53 (t, 2H, H-3, H-5, 8.6); 7.86÷7.76 (m, 2H, H-16, H-19); 7.33 (t, 1H, H-18, 7.7); 7.31 (d, 2H, H-9, H-11, 8.6); 6.99 (d, 2H, H-8, H-12, 8.6); 6.82 (t, 1H, H-17, 7.7).

^{13}C-NMR (dmso-d6, δ ppm): 152.29 (C-13); 139.78 (C-1); 139.46 (C-14); 136.47 (C-7); 131.52 (C-10); 91.36 (C-15); 138.91 (C-16); 128.56 (C-19); 125.07 (C-17); 122.05 (C-18); 132.76 (C-4); 129.17 (C-3, C-5); 126.67 (C-2, C-6); 122.14 (C-8, C-12); 118.83 (C-9, C-11).

FT-IR (solid in ATR, ν cm^{-1}): 3337w; 3305m; 3219vs; 3069w; 1663s; 1573m; 1544vs; 1509s; 1431m; 1392m; 1333m; 1283m; 1215m; 1157s; 1108m; 1013w; 912w; 792w; 734m; 719w; 682m; 650m.

Elemental analysis: Calculated: C 46.25%, H 3.27%, N 8.52%, S 6.5%; Found C 46.15%, H 3.5%, N 8.29%, S 6.3%.

Compound XIV: *N-[4-[(3-iodophenylcarbamoyl)-amino]phenyl]benzenesulfonamide*

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 10.02 (bs, 1H, H-α, deuterable); 8.74 (s, 1H, HN, H-γ, deuterable); 8.63 (s, 1H, HN, H-β, deuterable); 7.97 (t, 1H, H-15, 1.9); 7.71 (dd, 2H, H-2, H-6, 0.8, 8.6); 7.60 (tt, 1H, H-4, 0.8, 8.6); 7.53 (t, 2H, H-3, H-5, 8.6); 7.32÷7.27 (m, 2H, H-17, H-19); 7.29 (d, 2H, H-9, H-11, 8.6); 7.05 (t, 1H, H-18, 8.1); 6.98 (d, 2H, H-8, H-12, 8.6).

^{13}C-NMR (dmso-d6, δ ppm): 152.26 (C-13); 141.18 (C-1); 139.47 (C-14); 136.26 (C-7); 131.59 (C-10); 94.78 (C-16); 130.77 (C-15); 130.29 (C-17); 126.22 (C-19); 117.44 (C-18); 132.77 (C-4); 129.17 (C-3, C-5); 126.67 (C-2, C-6); 122.03 (C-8, C-12); 119.13 (C-9, C-11).

FT-IR (solid in ATR, ν cm^{-1}): 3316w; 3270m; 3093w; 1642s; 1604s; 1574m; 1551vs; 1506vs; 1472s; 1434m; 1393m; 1326m; 1300m; 1283m; 1216m; 1159vs; 1087m; 894m; 854w; 825w; 793w; 729m; 682m; 668m; 619m.

Elemental analysis: Calculated: C 46.25%, H 3.27%, N 8.52%, S 6.5%; Found C 46.39%, H 3.43%, N 8.33%, S 6.41%.

Compound XV: *N-[4-[(4-iodophenylcarbamoyl)-amino]phenyl]benzenesulfonamide*

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 10.02 (bs, 1H, H-α, deuterable); 8.72 (s, 1H, HN, H-γ, deuterable); 8.61 (s, 1H, HN, H-β, deuterable); 7.71 (dd, 2H, H-2, H-6, 0.8, 8.6); 7.60 (tt, 1H, H-4, 0.8, 8.6); 7.53 (t, 2H, H-3, H-5, 8.6); 7.57 (d, 2H, H-15, H-19, 9.1); 7.27 (d, 2H, H-16, H-18, 9.1); 7.29 (d, 2H, H-9, H-11, 8.6); 6.98 (d, 2H, H-8, H-12, 8.6).

^{13}C-NMR (dmso-d6, δ ppm): 152.28 (C-13); 139.58 (C-14); 139.48 (C-1); 136.34 (C-7); 131.52 (C-10); 84.62 (C-17); 132.75 (C-4); 137.31 (C-16, C-18); 129.16 (C-3, C-5); 126.66 (C-2, C-6); 122.06 (C-8, C-12); 120.42 (C-15, C-19); 119.03 (C-9, C-11).

FT-IR (solid in ATR, ν cm^{-1}): 3317m; 3239vs; 3056w; 1651s; 1598m; 1538vs; 1504s; 1483m; 1443w; 1389m; 1334m; 1304m; 1280m; 1214s; 1161s; 1089m; 1002w; 905w; 815w; 792w; 778w; 751w; 731m; 685w; 635m.

Elemental analysis: Calculated: C 46.25%, H 3.27%, N 8.52%, S 6.5%; Found C 46.41%, H 3.04%, N 8.31%, S 6.76%.

Conclusions

We obtained nine new derivatives of N-[4-[(phenylcarbamoyl)amino]phenyl]benzenesulfonamide using a new synthesis path, starting from the corresponding azide. The substances contain three important moieties: halogens, urea and sulfonamide groups that could determine a potential pharmacological effect. The chemical structures were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and elemental analysis.

In the near future we intend to investigate the pharmacological activity in order to identify the most valuable compound.

References

1. Bag S., Tulsan R., Sood A., Cho H., Redjeb H., Yhou W., Levine H., Torok B., Torok M., Sulfonamides as multifunctional agents for Alzheimer's disease. *Bioorg. Med. Chem. Letters*, 2015; 25: 626-630.
2. Boufas W., Dupont N., Berredjem M., Berrezag K., Becheker I., Berredjem H., Aouf N., Synthesis and antibacterial activity of sulfonamides. SAR and DFT studies. *Journal of Molecular Structure*, 2014; 1074: 180-185.
3. Chast F., A History of Drug Discovery, Academic Press, Second Edition, 2003; 17-18.
4. Constantin S., Buron F., Routier S., Confederat L., Iacob A.T., Miron A., Profire L., Studies on xanthine derivatives (II). Synthesis and antioxidant effects of some hydrazones with xanthine structure. *Farmacia*, 2016; 64(4): 565-571.
5. Jain P., Saravanan C., Singh S.K., Sulphonamides: Deserving class as MMP inhibitors?. *Eur. J. Med. Chem.*, 2013; 60: 89-100.
6. Kasimogullan R., Bulbul M., Arslan B.S., Gokce Basak, Synthesis, characterization and antiglaucoma activity of some novel pyrazole derivatives of 5-amino-1,3,4-thiadiazole-2-sulfonamide. *Eur. J. Med. Chem.*, 2010; 45: 4769-4773.
7. Limban C., Missir A.V., Nuță D.C., Căproiu M.T., Papacocea M.T., Chiriță C., Ssynthesis of some new 2-((4-chlorophenoxy)methyl)-n-(arylcarbamothioyl) benzamides as potential antifungal agents. *Farmacia*, 2016; 64(5): 775-779.
8. Moise M., Sunel V., Profire L., Popa M., Lionte C., Synthesis and antimicrobial activity of some new (sulfon-amidophenyl)-amide derivatives of N-(4-nitrobenzoyl)-phenylglycine and N-(4-nitrobenzoyl)-phenylalanine. *Farmacia*, 2008; LVI(3): 283-289.
9. Mukete B., Rosendorff C., Effects of low – dose thiazide diuretics on fasting plasma glucose and serum potassium – a meta – analysis, *J. Am. Soc. Hypertens.*, 2013; 7: 454-466.
10. Navakoski de Oliveira K., Costa P., Santin J.R., Mazzambani L., Burger C., Mora C., Nunes R.J., Maria de Souza M., Synthesis and antidepressant – like activity evaluation of sulphonamides and sulphonyl – hydrazones. *Bioorg. Med. Chem.*, 2011; 19: 4295-4306.
11. Organicum. Chimie organică practică (părțile A-C), Editura Ştiințifică şi Enciclopedică, București, 1982; 619.
12. Prete S., Vulloa D., De Luca V., Carginale V., Ferraroni M., Osman S., AlOthman Z., Supuran C., Capassp C., Sulfonamide inhibition studies of the β-carbonic anhydrase from the pathogenic bacterium *Vibrio cholerae*. *Bioorg. Med. Chem. Letters*, 2016; 24: 1115-1120.

13. Rosatelli E., Carotti A., Ceruso M., Supuran C., Gioiello A., Flow synthesis and biological activity of aryl sulfonamides as selective carbonic anhydrase IX and XII inhibitors. *Bioorg. Med. Chem. Letters*, 2014; 24: 3422-3425.

14. Sikka P., Sahu J.K., Mishra A.K., Hashim S.R., Role of Aryl Urea Containing Compounds in Medicinal Chemistry. *Med. Chem.*, 2015; 5: 11.