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Acid-catalyzed reaction of phenols with *N*-(4,4-diethoxybutyl)sulfonamides – a new method for the synthesis of 2-aryl-1-sulfonylpyrrolidines

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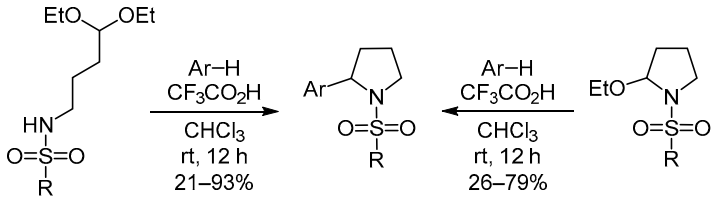


We have developed a new method for the synthesis of 2-aryl-1-sulfonylpyrrolidines on the basis of reactions between various phenols and *N*-(4,4-diethoxybutyl)sulfonamides in the presence of trifluoroacetic acid. The structures of the obtained products were confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, and X-ray structural analysis.

Keywords: 2-aryl-1-sulfonylpyrrolidines, *N*-(4,4-diethoxybutyl)sulfonamides, 2-ethoxypyrrolidines, phenols, sulfonyl chlorides.

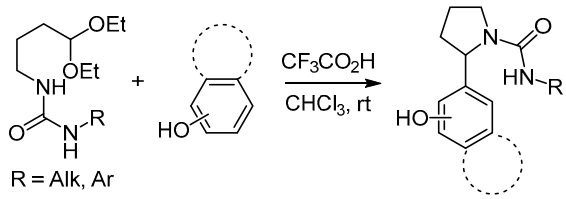
Pyrrolidine derivatives containing sulfonamide and aryl groups represent an important class of organic compounds, which includes many compounds with high pharmacological activity. 2-Aryl-1-sulfonylpyrrolidine derivatives can be used as drugs for the treatment and prevention of thromboembolism[1,2] and neurodegenerative conditions, such as Huntington's, Parkinson's,[3,4] and Alzheimer's[5] diseases. According to published data, such compounds are also able to inhibit matrix metalloproteinase 2.[6]

The most common approach to the synthesis of 2-aryl-1-sulfonylpyrrolidines is intramolecular cyclization of aryl-substituted unsaturated compounds containing a sulfonamide group. Such examples include the cyclization of 3-buten-1-amine,[7–14] 3-butyn-1-amine,[15] and 4-penten-1-amine[16–18] derivatives. These compounds have been synthesized by oxidative cyclization of sulfonamides,[19–22] carbonylation of *N*-tosylpentenamine derivatives,[23,24] or the reaction of 2-arylpyrrolidines with sulfonyl chlorides.[25] The most frequently used catalysts of such reactions are palladium(II)[7,8,21] or rhodium salts,[24] as well as hypervalent iodine compounds.[14,19–21] Common drawbacks of the existing methods for the synthesis of 2-aryl-1-sulfonylpyrrolidines include the use of costly catalysts and reagents, harsh reaction conditions, and the often laborious synthesis of the starting compounds. Thus, the development of a new and effective method for the synthesis of 2-aryl-1-sulfonylpyrrolidines would be of significant interest.

We have previously developed a method for the synthesis of 2-aryl-1-carboxamidopyrrolidines, based on a trifluoroacetic acid-catalyzed reaction between 4,4-diethoxybutylureas and phenols, allowing to obtain the target compounds in high yields under mild conditions (Scheme 1).[26–30]

Since the amide and sulfonamide groups are isosteric and have similar electronic properties, we proposed that the use of *N*-(4,4-diethoxybutyl)sulfonamides in this reaction instead of 4,4-diethoxybutylureas should enable us to perform the synthesis of 2-aryl-1-sulfonylpyrrolidines. Our expectations were additionally confirmed by published reports[31,32] on the formation of heterocyclic products upon

Scheme 1



the interaction of 4,4-diethoxybutan-1-amine with arylsulfonyl chlorides.

Synthesis of the starting *N*-(4,4-diethoxybutyl)arylsulfonamides **1a**,**b** was accomplished according to a previously described method[33] based on the reaction of 4,4-diethoxybutan-1-amine with *p*-toluene- and benzenesulfonyl chlorides in the presence of triethylamine (Scheme 2). Besides that, we additionally obtained *N*-(4,4-diethoxybutyl)alkylsulfonamides **1c**,**d** in order to identify the effects associated with the nature of substituents at the sulfur atom on the feasibility of intramolecular cyclization of these compounds.

The obtained acetal **1a** was involved in reactions with 4-chlororesorcinol, 2-naphthol, and 2,7-dihydroxynaphthalene in $CHCl_3$, which was accomplished in the presence of an equimolar amount of trifluoroacetic acid (Scheme 2). The products of this reaction were identified as the respective 2-aryl-1-*p*-toluenesulfonylpyrrolidines **2a**, **3a**, and **4a** (Table 1).

At the next stage of our study we performed reactions of 4-chlororesorcinol, 2-naphthol, and 2,7-dihydroxynaphthalene with acetals **1b**–**d**. The respective pyrrolidine derivatives **2c**,**d**, **3c**,**d**, and **4c**,**d** were obtained in yields that varied from 21 to 93% (Table 1). It should be noted that, according to NMR spectral data, the content of 2-arylpyrrolidines **2a**,**c**,**d**, **3a**,**c**,**d**, and **4a**,**c**,**d** in the reaction mixtures was in the range from 80 to 95%, while the structural and electronic features of the starting *N*-(4,4-diethoxybutyl)sulfonamides and phenols did not exert a clearly pronounced effect on the course of this reaction. The marked differences in the yields of individual compounds were linked to their different solubility affecting the losses during purification.

According to spectral data, compounds **2b**, **3b**, and **4b** were present in the reaction mixture in trace amounts, and thus could not be isolated as individual samples.

According to the literature data, 2-alkoxypyrrolidines in the presence of Lewis acids are able to undergo substitution reactions with organosilicon compounds,[34–38] alkenes activated by the presence of electron-withdrawing groups,[39,40] carbonyl compounds,[41,42] and sterically hindered phenols,[43] leading to formation of the corresponding 2-substituted pyrrolidine derivatives.

We anticipated that the use of 2-ethoxy-1-sulfonylpyrrolidines **5** instead of the respective acetals **1** in this reaction should also lead to the formation of 2-aryl-1-sulfonylpyrrolidines **2**–**4** (Scheme 2).

A method for the preparation of 2-ethoxy-1-tosylpyrrolidine by the cyclization of *N*-(4,4-diethoxybutyl)-4-methylbenzenesulfonamide under acidic conditions has been described in the literature.[33] As a result of our studies, conditions were selected that allowed to obtain 2-ethoxypyrrolidine **5a** in a single step, without isolation of the intermediate acetal **1a**. Analogous synthesis provided access to *N*-benzenesulfonyl-2-ethoxypyrrolidine **5b** (Scheme 2).

Scheme 2

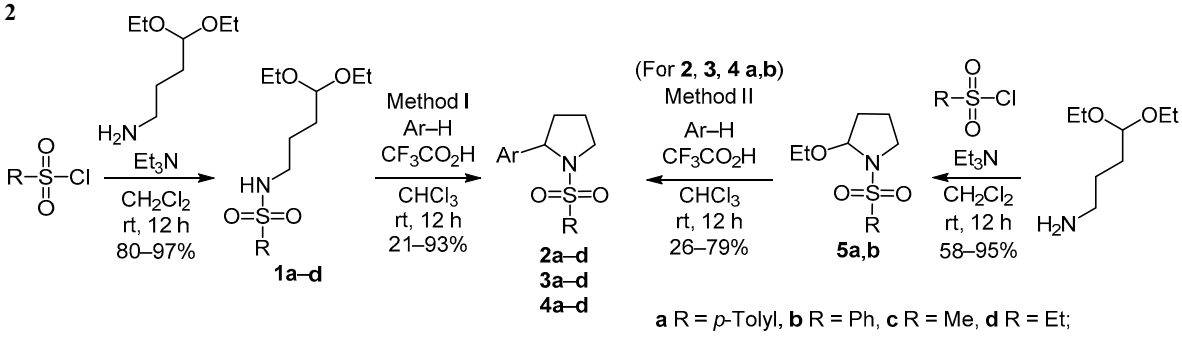
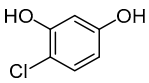
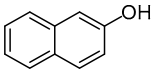
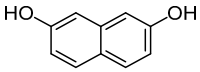
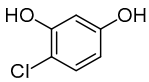
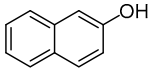
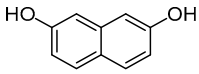


Table 1. Yields of products from the reactions of phenols with acetals **1a**–**d**

Phenol	Sulfonamide	Product	Yield, %
	**1a**	**2a**	43
	1b	**2b**	–*
	1c	**2c**	82
	1d	**2d**	45
	**1a**	**3a**	93
	1b	**3b**	–*
	1c	**3c**	93
	1d	**3d**	21
	**1a**	**4a**	71
	1b	**4b**	–*
	1c	**4c**	62
	1d	**4d**	40

*The product could not be isolated as individual compound.

Table 2. Yields of products from the reactions of phenols with 2-ethoxy-1-tosylpyrrolidines **5a**,**b**

Phenol	Pyrrolidine	Product	Yield, %
	**5a**	**2a**	53
	5b	**2b**	79
	**5a**	**3a**	71
	5b	**3b**	64
	**5a**	**4a**	34
	5b	**4b**	26

It was established that the reactions of 2-ethoxypyrrolidine **5a** with 4-chlororesorcinol, 2-naphthol, and 2,7-dihydroxynaphthalene in $CHCl_3$ solution in the presence of trifluoroacetic acid led to the formation of the respective 2-aryl-1-sulfonylpyrrolidines **2a**, **3a**, and **4a** (Scheme 2, Table 2). It should be noted that the reaction of 2-ethoxypyrrolidine **5b** with the corresponding phenols allowed to obtain compounds **2b**, **3b**, and **4b** in 26–79% yields. Similarly to the case of acetals **1a**–**d**, the difference in yields of the individual compounds **2a**,**b**, **3a**,**b**, and **4a**,**b** could be explained largely by the losses during the isolation and purification of the products, rather than by the nature of the starting materials.

The structures of the obtained compounds were confirmed by ^1H and ^{13}C NMR, as well as IR spectroscopy. The spatial structure of compound **3a** was established by X-ray structural analysis of crystals obtained after recrystallization from DMSO. As shown by the data of X-ray structural analysis, the bond lengths, bond angles, and torsion angles were within the typical limits for each type of bond (Fig. 1). An interesting feature in the molecular structure of this compound was the formation of a $C_1C_2O_{23}H_{23}N_1C_{11}$ "pseudoring" in the plane of the naphthalene system due to the OH···N type intramolecular hydrogen bond O(23)–H(23)···N(1) (the H(23)···N(1) distance 1.80(6) Å, O(23)···N(1) distance 2.647(6) Å, O(23)–H(23)···N(1) angle 155(5)°). The molecular packing in the crystal structure (Fig. 2) consisted of layers formed by CH···O interactions involving the oxygen atoms of SO_2 groups (the C···O distances were equal to 3.249(6) and 3.448(7) Å) and π–π-interactions between the benzene and naphthol rings (the distances between the planes of interacting aromatic rings were 3.0–3.7 Å).

Thus, the reactions of *N*-(4,4-diethoxybutyl)sulfonamides with phenols of benzene series, as well as with naphthols under mild conditions allowed to obtain 2-aryl-1-sulfonylpyrrolidines containing both aromatic and aliphatic substituents at the sulfonamide group.

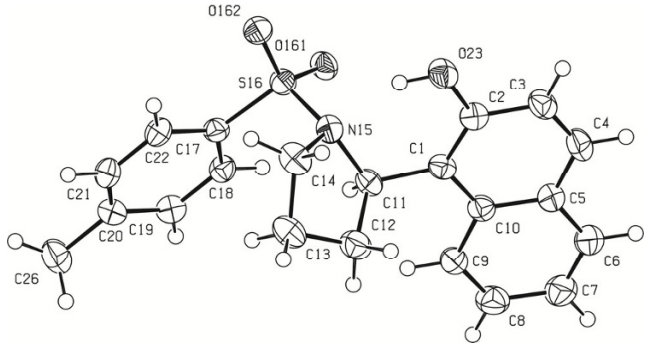


Figure 1. The molecular structure of compound **3a** with atoms represented by thermal vibration ellipsoids of 50% probability.

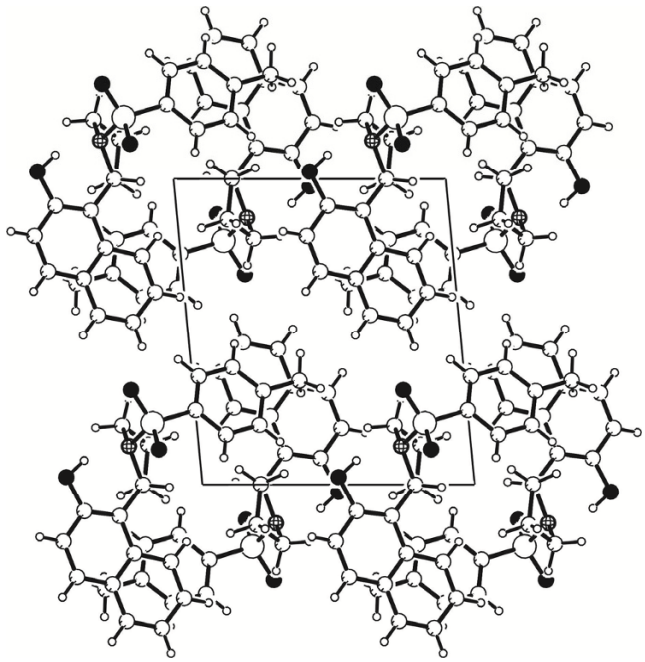


Figure 2. Molecular packing in crystals of compound **3a**.

Experimental

IR spectra were recorded on a UR-20 spectrometer (400–3600 cm^{-1}) in KBr pellets. ^1H NMR spectra were acquired on a Bruker MSL 400 spectrometer (400 MHz) in DMSO-d_6, $CDCl_3$, and CD_3OD. Internal standard – residual proton signals of the deuterated solvents (δ 2.50 ppm in DMSO-d_6, δ 7.26 ppm in $CDCl_3$, δ 3.31 ppm in CD_3OD). ^{13}C NMR spectra were acquired on a Bruker Avance 600 spectrometer (150 MHz) in DMSO-d_6, $CDCl_3$, and CD_3OD. Internal standard – ^{13}C NMR signals of the solvent molecules (δ 39.5 for DMSO-d_6, δ 77.0 for $CDCl_3$, δ 49.0 ppm for CD_3OD). Elemental analysis was performed on a Carlo Erba EA 1108 instrument. Schöniger method was applied for chlorine and sulfur determination.[44] Melting points were determined in glass capillaries, by using a Stuart SMP 10 digital melting point apparatus.

Synthesis of *N*-(4,4-diethoxybutyl)sulfonamides 1a–d (General method). 4,4-Diethoxybutan-1-amine (3.4 g, 20 mmol) was added to a cooled (5–8°C) solution of the appropriate sulfonyl chloride (20 mmol) and Et_3N (3.5 ml) in CH_2Cl_2 (100 ml). The reaction mixture was stirred at room temperature for 12 h, then washed with saturated $NaHCO_3$ solution (100 ml), the organic layer was separated and the residual solvents were removed under reduced pressure.

***N*-(4,4-Diethoxybutyl)-4-methylbenzenesulfonamide (1a)**. Yield 6.20 g (93%), yellow oil. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.19 (6H, t, *J* = 7.1, $2CH_3$); 1.54–1.64 (4H, m, $2CH_2$); 2.44 (3H, s, CH_3); 2.94–3.01 (2H, m, CH_2); 3.42–3.51 (2H, m, CH_2); 3.58–3.66 (2H, m, CH_2); 4.42 (1H, t, *J* = 5.1, CH); 4.88 (1H, br. s, NH); 7.31 (2H, d, *J* = 8.0, H Ar); 7.76 (2H, d, *J* = 8.2, H Ar).

***N*-(4,4-Diethoxybutyl)benzenesulfonamide (1b)**. Yield 4.82 g (80%), yellow oil. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.11 (6H, t, *J* = 7.1, $2CH_3$); 1.44–1.59 (4H, m, $2CH_2$); 2.92 (2H, q, *J* = 6.5, CH_2); 3.35–3.42 (2H, m, CH_2); 3.50–3.59 (2H, m, CH_2); 4.36 (1H, t, *J* = 5.1, CH); 5.41 (1H, s, NH); 7.44 (2H, t, *J* = 7.7, H Ph); 7.50 (1H, t, *J* = 7.4, H Ph); 7.81 (2H, d, *J* = 7.7, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 15.2; 15.3; 24.6; 30.8; 43.1; 61.4; 102.5; 126.9; 129.0; 132.4; 140.2.

***N*-(4,4-Diethoxybutyl)methanesulfonamide (1c)**. Yield 3.76 g (97%), yellow oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.97 (6H, t, *J* = 7.1, $2CH_3$); 1.35–1.51 (4H, m, $2CH_2$); 2.72 (3H, s, CH_3); 2.84–2.93 (2H, m), 3.21–3.33 (2H, m) and 3.36–3.50 (2H, m, $3CH_2$); 4.23–4.31 (1H, m, CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 15.1; 24.9; 30.6; 39.6; 42.8; 61.2; 102.4.

***N*-(4,4-Diethoxybutyl)ethanesulfonamide (1d)**. Yield 4.60 g (90%), yellow oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.17 (6H, t, *J* = 7.1, $2CH_3$); 1.20 (3H, t, *J* = 7.5, CH_3); 1.45–1.59 (4H, m), 2.89 (2H, q, *J* = 7.4), 2.96 (2H, q, *J* = 5.9), 3.29–3.41 (2H, m), and 3.45–3.58 (2H, m, $6CH_2$); 4.34 (1H, t, *J* = 5.1, CH); 5.12 (1H, t, *J* = 5.4, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 8.1; 15.2; 25.2; 30.7; 42.8; 46.5; 61.3; 102.4.

Synthesis of 2-ethoxypyrrolidines 5a,b (General method). The appropriate sulfonyl chloride (20 mmol) was added with cooling (5–8°C) to a solution of 4,4-diethoxybutan-1-amine (3.4 g, 20 mmol) and Et_3N (3.5 ml) in CH_2Cl_2 (100 ml). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then washed with saturated aqueous $NaHCO_3$ solution (100 ml), the organic layer was separated, and the solvent was removed under reduced pressure.

2-Ethoxy-1-tosylpyrrolidine (5a). Yield 2.21 g (58%), beige powder, mp 85–86°C. IR spectrum, ν, cm^{-1}: 1161 (SO_2), 1596 (CH Ar). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.20 (3H, t, *J* = 7.0, CH_3); 1.35–1.52 (1H, m), 1.69–1.80 (1H, m), 1.82–1.92 (1H, m), and 1.95–2.09 (1H, m, $2CH_2$); 2.44 (3H, s, CH_3); 3.09–3.20 (1H, m), 3.37–3.44 (1H, m), 3.54–3.60 (1H, m), and 3.78–3.84 (1H, m, $2CH_2$); 5.20–5.25 (1H, m, CH); 7.32 (2H, d, *J* = 8.1, H Ar); 7.74 (2H, d, *J* = 8.2, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 15.0; 21.5; 23.2; 32.9; 47.2; 63.1; 90.2; 127.4; 129.6; 136.1; 143.3. Found, %: C 58.09; H 7.23; N 5.07; S 11.81. $C_{13}H_{19}NO_3S$. Calculated, %: C 57.97; H 7.11; N 5.20; S 11.90.

2-Ethoxy-1-(phenylsulfonyl)pyrrolidine (5b). Yield 4.59 g (95%), beige powder, mp 81–82°C. IR spectrum, ν, cm^{-1}: 1156 (SO_2), 1585 (CH Ar). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.11 (3H, t, *J* = 7.1, CH_3); 1.30–1.42 (1H, m), 1.64–1.73 (1H, m), 1.76–1.85 (1H, m), 1.90–2.07 (1H, m), 3.06–3.15 (1H, m), 3.30–3.40 (1H, m), 3.42–3.53 (1H, m), and 3.68–3.78 (1H, m, $4CH_2$); 5.12–5.20 (1H, m, CH); 7.39–7.47 (2H, m, H Ph); 7.48–7.56 (1H, m, H Ph); 7.75–7.82 (2H, m, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 15.0; 23.2; 32.9; 47.3; 63.1; 90.2; 127.3; 129.0; 132.6; 139.0. Found, %: C 58.18; H 7.28; N 5.31; S 12.71. $C_{13}H_{19}NO_3S$. Calculated, %: C 57.97; H, 7.11; N 5.20; S 12.56.

Synthesis of 2-aryl-1-sulfonylpyrrolidines 2–4 (General methods). Method I. The appropriate phenol (0.80 mmol) and trifluoroacetic acid (0.12 ml, 1.59 mmol) were added to a solution of *N*-(4,4-diethoxybutyl)sulfonamide **1** (1.59 mmol) in $CHCl_3$ (10 ml). The reaction mixture was stirred for 12 h at room temperature. The solvent was then removed at reduced pressure, the residue was washed with Et_2O and the solids were filtered off. The product was isolated as white powder, which was dried under vacuum.

Method II. The appropriate phenol (0.93 mmol) and trifluoroacetic acid (0.14 ml, 1.86 mmol) were added to a solution of 2-ethoxy-1-pyrrolidine **5** (1.86 mmol) in $CHCl_3$ (10 ml). The reaction mixture was stirred at room temperature for 12 h. The solvent was then removed at reduced pressure, the residue was washed with Et_2O and the solids were filtered off. The product was isolated as a white powder that was dried under vacuum.

4-Chloro-6-(1-tosylpyrrolidin-2-yl)benzene-1,3-diol (2a). Yield 0.25 g (43%, method I), 0.36 g (53%, method II), white powder, mp 144–145°C. IR spectrum, ν, cm^{-1}: 1152 (SO_2), 1598 (CH Ar), 3422 (O–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.54–1.63 (1H, m) and 1.67–1.88 (3H, m, $2CH_2$); 2.41 (3H, s, CH_3); 3.31–3.39 (1H, m) and 3.55–3.63 (1H, m, CH_2); 4.92–4.97 (1H, m, CH); 6.42 (1H, s, H Ar); 7.11 (1H, s, H Ar); 7.36 (2H, d, *J* = 8.0, H Ar); 7.70 (2H, d, *J* = 8.3, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.2; 23.4; 33.7; 49.2; 58.4; 103.2; 110.3; 122.6; 127.3; 127.7; 129.4; 134.5; 143.8; 152.1; 153.1. Found, %: C 55.70; H 5.15; Cl 9.47; N 3.93; S 8.56. $C_{17}H_{18}ClNO_4S$. Calculated, %: C 55.51; H 4.93; Cl 9.64; N 3.81; S 8.72.

1-(1-Tosylpyrrolidin-2-yl)naphthalen-2-ol (3a). Yield 0.54 g (93%, method I), 0.48 g (71%, method II), white powder, mp 162–163°C. IR spectrum, ν, cm^{-1}: 1162 (SO_2), 1598 (CH Ar), 3200, 3438 (O–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.23–1.37 (1H, m), 1.87–1.97 (1H, m) and 2.00–2.21 (2H, m, $2CH_2$); 2.41 (3H, s, CH_3); 3.59–3.67 (1H, m) and 3.70–3.81 (1H, m, CH_2); 5.37–5.44 (1H, m, CH); 7.16 (1H, d, *J* = 8.8, H Ar); 7.29 (1H, t, *J* = 7.4, H Ar); 7.40 (2H, d, *J* = 7.0, H Ar); 7.46 (1H, t, *J* = 7.3, H Ar); 7.69 (1H, d, *J* = 8.8, H Ar); 7.73 (2H, d, *J* = 8.1, H Ar); 7.79 (1H, d, *J* = 7.9, H Ar); 8.15 (1H, d, *J* = 8.7, H Ar); 9.81 (1H, s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.5; 25.5; 32.8; 50.1; 56.9; 118.7; 118.8; 122.6; 123.7; 126.3; 128.0; 129.1 (2C); 129.2; 130.0; 132.4; 134.4; 143.6; 153.2. Found, %: C 68.71; H 5.65; N 3.93; S 8.66. $C_{21}H_{21}NO_3S$. Calculated, %: C 68.64; H 5.76; N 3.81; S 8.72.

1-(1-Tosylpyrrolidin-2-yl)naphthalene-2,7-diol (4a). Yield 0.43 g (71%, method I), 0.24 g (34%, method II), white powder, mp 168–169°C. IR spectrum, ν, cm^{-1}: 1156 (SO_2), 1597 (CH Ar), 3423 (O–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.17–1.28 (1H, m), 1.86–2.02 (2H, m), and 2.05–2.17 (1H, m, $2CH_2$); 2.42 (3H, s, CH_3); 3.59–3.68 (1H, m) and 3.79–3.89 (1H, m, CH_2); 5.28–5.37 (1H, m, CH); 6.85 (1H, dd, ^3J = 8.7, ^4J = 2.2, H Ar); 6.90 (1H, d, *J* = 8.7, H Ar); 7.38 (1H, d, *J* = 2.0, H Ar); 7.40 (2H, d, *J* = 6.6, H Ar); 7.52 (1H, d, *J* = 8.7, H Ar); 7.61 (1H, d, *J* = 8.8, H Ar); 7.78 (2H, d, *J* = 7.9, H Ar); 9.63 (1H, br. s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.5; 25.4; 32.3; 50.1; 56.9; 106.0; 115.0; 115.3; 117.0; 123.8; 128.1; 128.9; 130.0; 130.6; 133.9; 134.3; 143.5; 153.5; 155.6. Found, %: C 65.61; H 5.65; N 3.53; S 8.40. $C_{21}H_{21}NO_4S$. Calculated, %: C 65.78; H 5.52; N 3.65; S 8.36.

4-Chloro-6-[1-(methylsulfonyl)pyrrolidin-2-yl]benzene-1,3-diol (2c) was obtained according to the method I. Yield 0.38 g (82%), white powder, mp 227–230°C. IR spectrum, ν, cm^{-1}: 1152 (SO_2), 1600 (CH Ar), 3390, 3439 (O–H).

^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.59–1.95 (3H, m) and 2.07–2.26 (1H, m, $2CH_2$); 2.89 (3H, s, CH_3); 3.30–3.44 (2H, m, CH_2); 4.77–4.89 (1H, m, CH); 6.49 (1H, s, H Ar); 7.06 (1H, s, H Ar); 9.61 (1H, s, OH); 9.78 (1H, s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 24.1; 34.1; 34.5; 49.3; 58.2; 104.0; 109.5; 122.9; 127.8; 152.5; 153.5. Found, %: C 45.05; H 4.69; Cl 12.34; N 5.01; S 11.17. $C_{11}H_{14}ClNO_4S$. Calculated, %: C 45.28; H 4.84; Cl 12.15; N 4.80; S 10.99.

1-[1-(Methylsulfonyl)pyrrolidin-2-yl]naphthalen-2-ol (3c) was obtained according to the method I. Yield 0.43 g (93%), white powder, mp 183–184°C. IR spectrum, ν, cm^{-1}: 1129 (SO_2), 1583 (CH Ar), 2972, 3063, 3383 (O–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.91–2.02 (1H, m), 2.04–2.12 (1H, m), 2.16–2.24 (1H, m), and 2.25–2.32 (1H, m, $2CH_2$); 2.83 (3H, s, CH_3); 3.66–3.74 (2H, m, CH_2); 5.55–5.64 (1H, m, CH); 7.15 (1H, d, *J* = 8.8, H Ar); 7.28 (1H, t, *J* = 7.4, H Ar); 7.44 (1H, t, *J* = 7.1, H Ar); 7.68 (1H, d, *J* = 8.8, H Ar); 7.78 (1H, d, *J* = 7.8, H Ar); 8.18 (1H, d, *J* = 8.7, H Ar); 9.78 (1H, s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 25.9; 33.1; 34.9; 49.7; 56.9; 118.9; 119.1; 122.6; 123.6; 126.3; 128.9; 129.0; 129.2; 132.6; 153.2. Found, %: C 61.71; H 6.03; N 4.95; S 10.82. $C_{15}H_{17}NO_3S$. Calculated, %: C 61.83; H 5.88; N 4.81; S 11.01.

1-[1-(Methylsulfonyl)pyrrolidin-2-yl]naphthalene-2,7-diol (4c) was obtained according to the method I. Yield 0.30 g (62%), white powder, mp 175–176°C. IR spectrum, ν, cm^{-1}: 1129 (SO_2), 1590 (CH Ar), 2926, 2977, 3258, 3421 (O–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.89–2.01 (1H, m) and 2.03–2.12 (1H, m, CH_2); 2.15–2.30 (2H, m, CH); 2.79 (3H, s, CH_3); 3.65–3.81 (2H, m, CH_2); 5.44–5.53 (1H, m, CH); 6.85 (1H, dd, ^3J = 8.7, ^4J = 2.2, H Ar); 7.00 (1H, d, *J* = 8.8, H Ar); 7.39 (1H, d, *J* = 1.9, H Ar); 7.52 (1H, d, *J* = 8.8, H Ar); 7.60 (1H, d, *J* = 8.8, H Ar); 9.55 (1H, s, OH); 9.61 (1H, s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 25.8; 32.7; 35.1; 49.6; 56.9; 105.9; 115.0; 115.4; 116.9; 123.7; 128.9; 130.6; 134.1; 153.5; 155.7. Found, %: C 58.81; H 5.33; N 4.75; S 10.29. $C_{15}H_{17}NO_4S$. Calculated, %: C 58.62; H 5.58; N 4.56; S 10.43.

4-Chloro-6-[1-(ethylsulfonyl)pyrrolidin-2-yl]benzene-1,3-diol (2d) was obtained according to the method I. Yield 0.22 g (45%), white powder, mp 171–172°C. IR spectrum, ν, cm^{-1}: 1140 (SO_2), 1600 (CH Ar), 3406, 3456 (O–H). ^{1}H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 1.31 (3H, t, *J* = 7.4, CH_3); 1.85–2.02 (3H, m), 2.21–2.34 (1H, m), 3.01 (2H, q, *J* = 7.4), and 3.54–3.60 (2H, m, $4CH_2$); 5.01–5.08 (1H, m, CH); 6.44 (1H, s, H Ar); 7.16 (1H, s, H Ar). ^{13}C NMR spectrum (CD_3OD), δ, ppm: 6.7; 24.0; 33.9; 43.8; 48.8; 58.3; 103.4; 110.2; 122.5; 127.8; 152.3; 153.3. Found, %: C 47.33; H 5.12; Cl 11.70; N 4.38; S 10.64. $C_{12}H_{16}ClNO_4S$. Calculated, %: C 47.14; H 5.27; Cl 11.59; N 4.58; S 10.49.

1-[1-(Ethylsulfonyl)pyrrolidin-2-yl]naphthalen-2-ol (3d) was obtained according to the method I. Yield 0.10 g (21%), white powder, mp 176–177°C. IR spectrum, ν, cm^{-1}: 1139 (SO_2), 1582 (CH Ar), 2882, 2969, 3409 (O–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.07 (3H, t, *J* = 7.3, CH_3); 1.85–2.00 (1H, m), 2.04–2.13 (1H, m), 2.19–2.33 (2H, m), 2.71–2.86 (2H, m), 3.64–3.71 (1H, m), and 3.76–3.83 (1H, m, $4CH_2$); 5.62–5.75 (1H, m, CH); 7.16 (1H, d, *J* = 8.8, H Ar); 7.28 (1H, t, *J* = 7.4, H Ar); 7.44 (1H, t, *J* = 7.3, H Ar); 7.69 (1H, d, *J* = 8.8, H Ar); 7.78 (1H, d, *J* = 7.9, H Ar); 8.14 (1H, d, *J* = 8.7, H Ar); 9.80 (1H, s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 8.0; 26.5; 33.1; 44.1; 49.6; 56.5; 118.7; 118.9; 122.6; 123.4; 126.4; 128.9; 129.0; 129.3; 132.7; 153.4. Found, %: C 63.18; H 6.15; N 4.77; S 10.49. $C_{16}H_{19}NO_3S$. Calculated, %: C 62.93; H 6.27; N 4.59; S 10.57.

1-[1-(Ethylsulfonyl)pyrrolidin-2-yl]naphthalene-2,7-diol (4d) was obtained according to the method I. Yield 0.20 g (40%), white powder, mp 118–120°C. IR spectrum, ν, cm^{-1}: 1141 (SO_2), 1592 (CH Ar), 3411 (O–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.06 (3H, t, *J* = 7.3, CH_3); 1.84–2.01 (1H, m), 2.04–2.13 (1H, m), 2.16–2.32 (2H, m), 2.67–2.85 (2H, m), and 3.67–3.86 (2H, m, $4CH_2$); 5.55–5.67 (1H, m, CH); 6.84 (1H, d, *J* = 6.9, H Ar); 6.90 (1H, d, *J* = 8.5, H Ar); 7.36 (1H, s, H Ar); 7.52 (1H, d, *J* = 8.8, H Ar); 7.60 (1H, d, *J* = 8.8, H Ar); 9.56 (1H, s, OH); 9.62 (1H, s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 8.0; 26.3; 32.8; 44.3; 49.4; 56.5; 105.6; 115.1; 115.4; 116.7; 123.6; 129.1; 130.6; 131.6; 134.1; 153.7; 155.7. Found, %: C 59.95; H 6.11; N 4.51; S 10.18. $C_{16}H_{19}NO_4S$. Calculated, %: C 59.79; H 5.96; N 4.36; S 9.98.

4-Chloro-6-[1-(phenylsulfonyl)pyrrolidin-2-yl]benzene-1,3-diol (2b) was obtained according to the method II. Yield 0.52 g (79%), white powder, mp 148–150°C. IR spectrum, ν, cm^{-1}: 1150 (SO_2), 1602 (CH Ar), 3438, 3611 (O–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.41–1.52 (1H, m), 1.56–1.75 (3H, m), 3.20–3.29 (1H, m), and 3.51–3.63 (1H, m, $3CH_2$); 4.75–4.84 (1H, m, CH); 6.51 (1H, s, H Ar); 7.06 (1H, s, H Ar); 7.65 (2H, t, *J* = 7.2, H Ar); 7.72 (1H, t, *J* = 7.3, H Ar); 7.81 (2H, d, *J* = 7.0, H Ar); 9.64 (1H, s, OH); 9.82 (1H, s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 23.8; 34.0; 49.6; 58.4; 104.0; 109.6; 122.5; 127.6; 127.9; 129.9; 133.5; 137.5; 152.7; 153.5. Found, %: C 54.47; H 4.39; Cl 9.86; N 3.80; S 9.22. $C_{16}H_{16}ClNO_4S$. Calculated, %: C 54.31; H 4.56; Cl 10.02; N 3.96; S 9.06.

1-[1-(Phenylsulfonyl)pyrrolidin-2-yl]naphthalen-2-ol (3b) was obtained according to the method II. Yield 0.42 g (64%), white powder, mp 84–86°C. IR spectrum, ν, cm^{-1}: 1159 (SO_2), 1585 (CH_{Ar}), 3411 (O–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.55–1.73 (1H, m), 2.00–2.12 (1H, m), 2.16–2.37 (2H, m) and 3.79–3.87 (2H, m, $3CH_2$); 5.58–5.67 (1H, m, CH); 7.00 (1H, d, *J* = 8.8, H Ar); 7.29–7.23 (1H, m, H Ar); 7.39–7.46 (3H, m, H Ar); 7.52–7.58 (1H, m, H Ar); 7.61 (1H, d, *J* = 8.8, H Ar); 7.68–7.76 (3H, m, H Ar); 8.14 (1H, d, *J* = 8.7, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 25.1; 32.4; 49.5; 57.1; 117.5; 117.6; 122.0; 122.7; 125.6; 127.4; 128.3; 128.4; 128.9; 129.2; 132.3 (2C); 137.5; 152.8. Found, %: C 68.18; H 5.19; N 3.83; S 8.87. $C_{16}H_{19}NO_4S$. Calculated, %: C 67.97; H 5.42; N 3.96; S 9.07.

1-[1-(Phenylsulfonyl)pyrrolidin-2-yl]naphthalene-2,7-diol (4b) was obtained according to the method II. Yield 1.18 g (26%), white powder, mp 118–119°C. IR spectrum,

ν, cm^{-1}: 1155 (SO_2), 1598 (CH Ar), 3278, 3424 (O–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.19–1.30 (1H, m), 1.86 (2H, m), 2.07–2.18 (1H, m), 3.63–3.73 (1H, m), and 3.78–3.89 (1H, m, $3CH_2$); 5.30–5.42 (1H, m, CH); 6.84 (1H, dd, *J* = 8.7, *J* = 2.2, H Ar); 6.89 (1H, d, *J* = 8.6, H Ar); 7.38 (1H, s, H Ar); 7.51 (1H, d, *J* = 8.7, H Ar); 7.58–7.65 (4H, m, H Ar); 7.69 (1H, t, *J* = 7.4, H Ar); 7.87 (1H, d, *J* = 7.6, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 25.4; 32.3; 50.1; 57.0; 115.0; 115.3; 117.0; 117.0; 123.9; 126.6; 128.0; 129.0; 129.4; 129.5; 130.7; 133.3; 153.6; 155.6. Found, %: C 65.16; H 4.97; N 3.98; S 8.55. $C_{20}H_{19}NO_4S$. Calculated, %: C 65.02; H 5.18; N 3.79; S 8.68.

Monocrystal X-ray structural study of compound 3a was performed on a Bruker SMART Apex II diffractometer (graphite monochromator, λ(MoKα) 0.71073 Å). Crystals of compound **3a** ($C_{21}H_{21}NO_3S$) were triclinic. At 20°C: *a* 8.315(12), *b* 9.836(14), *c* 11.323(16) Å, α 92.846(15), β 103.917(15), γ 99.573(16)°; *V* 882(2) $Å^3$; *Z* 2; d_{calc} 1.383 g/cm^3, space group $P\bar{1}$. The intensities of 6448 reflections were measured, of which 1081 were with $I \geq 2\sigma$. The final probability factors were *R* 0.0607, wR_2 0.1. The structure was solved and refined first in isotropic and then in anisotropic approximation by using the SHELXL-97 program.[45] Hydrogen atoms were placed in calculated positions. The visualization of molecules and analysis of intermolecular interactions were performed with the PLATON program.[46] X-ray structural analysis data for compound **3a** were deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1487182).

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