

Article

Synthesis of Novel Aryl(heteroaryl)sulfonyl Ureas of Possible Biological Interest

Franciszek Sączewski ^{1,*}, Anna Kuchnio ¹, Monika Samsel ¹, Marta Łobocka ¹,
Agnieszka Kiedrowska ¹, Karolina Lisewska ¹, Jarosław Sączewski ¹, Maria Gdaniec ²
and Patrick J. Bednarski ³

¹ Department of Chemical Technology of Drugs, Faculty of Pharmacy, Medical University of Gdańsk, 80-416 Gdańsk, Poland

² Faculty of Chemistry, A. Mickiewicz University, 60-780 Poznań, Poland

³ Department of Pharmaceutical and Medicinal Chemistry, Institute of Pharmacy, University of Greifswald, D-17487 Greifswald, Germany

* Author to whom correspondence should be addressed; E-Mail: saczew@gumed.edu.pl.

Received: 19 January 2010; in revised form: 26 February 2010 / Accepted: 26 February 2010 /

Published: 26 February 2010

Abstract: The course of reaction of aryl and heteroaryl sulfonamides with diphenylcarbonate (DPC) and 4-dimethylaminopyridine (DMAP) was found to depend on the pK_a of the sulfonamide used. Aryl sulfonamides with $pK_a \sim 10$ gave 4-dimethylaminopyridinium arylsulfonyl-carbamoylides, while the more acidic heteroaryl sulfonamides ($pK_a \sim 8$) furnished 4-dimethylaminopyridinium heteroarylsulfonyl carbamates. Both the carbamoylides and carbamate salts reacted with aliphatic and aromatic amines with the formation of appropriate aryl(heteroaryl)sulfonyl ureas, and therefore, can be regarded as safe and stable substitutes of the hazardous and difficult to handle aryl(heteroaryl)sulfonyl isocyanates.

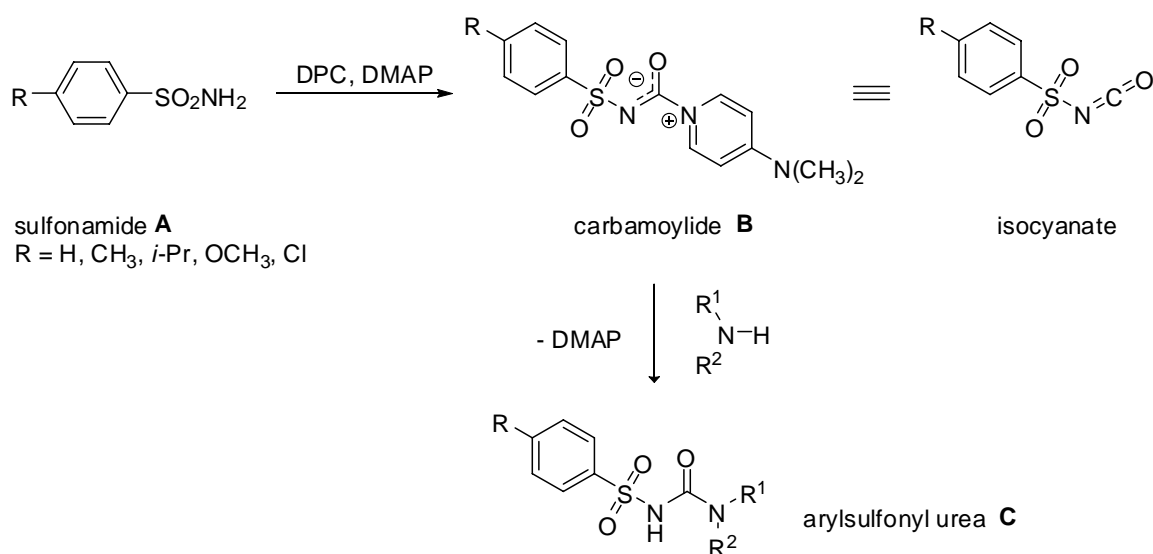
Keywords: 4-dimethylaminopyridinium arylsulfonylcarbamoylides; 4-dimethylaminopyridinium arylsulfonyl carbamates; arylsulfonyl ureas; heteroarylsulfonyl ureas; arylsulfonyl isocyanate substitutes

1. Introduction

Arylsulfonyl ureas constitute a well known class of compounds which exhibit a wide range of biological activities. The most important include: antidiabetic drugs (e.g., *glibenclamide*) [1], diuretic drugs (e.g., *torasemide*) [2], inhibitors of thromboxane synthase and thromboxane A2 receptor antagonists with antithrombotic properties [3,4] and inhibitors of acetohydroxyacid synthase (AHAS) which are used as herbicides (e.g., *chlorsulfuron*) or agents active against *Mycobacterium tuberculosis* [5,6] as well as antiischemic [7], antimalarial [8], antifungal [9] and oncolytic (e.g., *sulofenur*) [10] agents. Of special interest are antagonists of chemokine receptors (CXCR2 receptors) which are potential drugs for the treatment of acute respiratory distress syndrome, asthma, chronic bronchitis, pulmonary fibrosis and cystic fibrosis [11]. Therefore, for medicinal chemistry purposes an easy access to arylsulfonylureas is of great importance.

Recently, we have described a facile method for the preparation of arylsulfonyl ureas of general formula **C** (Scheme 1) using 4-dimethylaminopyridinium arylsulfonyl-carbamoylides **B**, which constitute non-hazardous substitutes of arylsulfonyl isocyanates [12,13]. As shown in Scheme 1, the method consists in the reaction of aromatic sulfonamides **A** with diphenyl carbonate (DPC) in the presence of 4-dimethylaminopyridine (DMAP), followed by the reaction with primary or secondary aliphatic or aromatic amine. The above procedure worked well with phenylsulfonamide and its *para*-substituted congeners, such as *p*-alkyl, *p*-methoxy- and *p*-chloro-phenylsulfonamide as the substrates. The unique structure of the carbamoylides obtained were confirmed by IR and NMR spectra as well as single crystal X-ray structure analysis [13]. Carbamoylides **B** compose of an appropriate arylsulfonyl isocyanate and a DMAP molecule. The stability of these highly polarizable adducts is mainly due to the delocalization of the positive charge on the pyridine ring and the negative charge on the arylsulfonylcarbamoyl moiety.

Scheme 1. 4-Dimethylaminopyridinium arylsulfonyl carbamoylides as stable substitutes of arylsulfonyl isocyanates.



In order to explore the scope of this procedure, an analogous previously not attempted reaction sequence starting from variously substituted phenylsulfonamides, naphthylsulfonamide as well as heteroarylsulfonamides, such as 2-thienyl- and benzothiazol-2-yl-sulfonamide has now been attempted.

2. Results and Discussion

The results of the investigations are presented in Scheme 2. First, it was found that the reaction of variously substituted phenylsulfonamides **1a-c** (including *p*-nitrophenyl-, *o*-chlorophenyl- and 2-naphthylsulfonamide) with DPC in the presence of DMAP proceeded smoothly at room temperature to give appropriate carbamoylides **3a-c** in good yields. The reactions of these stable arylsulfonyl isocyanates substitutes carried out in CH₃CN with both aliphatic and aromatic amines at elevated temperature afforded the desired arylsulfonyl ureas, which could be easily separated from the reaction mixtures upon treatment with 1% aqueous HCl.

However, when 2-thienyl and benzothiazol-2-yl-sulphonamides **1d-f** were treated with DPC in the presence of DMAP, the pyridinium carbamates **4a-c** were obtained as the sole products. Neither prolonged reaction times nor elevated temperatures changed the reaction course.

The structures of pyridinium carbamoylides **3** and pyridinium carbamates **4** were confirmed by IR and NMR spectroscopic data as well as X-ray single crystal structure analysis of **4b** and **4c** (Figure 1). The compounds **4b** and **4c** are organic salts with the proton transferred from the sulfonylcarbamate group to 4-dimethylaminopyridine. In the crystal the anions and the pyridinium cations form ionic pairs via N-H⁺⋯N⁻ hydrogen bonds. The anions assume similar conformation with one of the SO₂ group O atoms approximately in the plane of benzothiazole moiety and the bond lengths and angles are as expected. The crystal packing is, to a large extent, governed by electrostatic interactions, with a pair of 4-dimethylaminopyridinium cations stacked in anti-parallel manner and completely surrounded by the anions.

The major difference between the two classes of sulfonamide derivatives studied lies in their relative acidity, hence, it was reasoned that the more acidic heteroarylsulfonyl sulfonamides **1d-f** ($pK_a \sim 8$) [14] formed the more acidic carbamates **2d-f** which, in turn, suffered proton abstraction by DMAP to give pyridinium salts of carbamates **4a-c**, while the less acidic arylsulfonamides **1a-c** ($pK_a \sim 10$) [15] gave rise to the formation of less acidic carbamates **2a-c** which underwent nucleophilic substitution reaction with DMAP to give the desired carbamoylides **3a-c**.

In order to confirm the above hypothesis the reaction of DPC/DMAP couple with 4-chloropyridin-3-yl-sulfonamide (**1g**), characterized by a pK_a value of 8.9 [16], was performed. As shown in Scheme 3, the above reaction carried out at ambient temperature afforded two products: the carbamate pyridinium salt **4d** and the carbamoylide **3d** which could be separated from the reaction mixture by fractional crystallization in 48% and 39% yield, respectively. Interestingly enough, while the desired aryl(heteroaryl)sulfonyl ureas **5** and **6** were obtained in good yields from the reactions of either **3a-c** or **4a-c** with aliphatic, aromatic and heteroaromatic amines, upon treatment of both the carbamate **4d** and carbamoylide **3d** with an excess of a secondary amine, 3-(indolin-1-yl)pyrido[3,4-*e*][1,4,3]oxathiazine 1,1-dioxide (**8**) was obtained. This might be formed as a result of an intramolecular nucleophilic substitution reaction in the transiently formed arylsulfonyl ureidate **7** (Scheme 3).

All the newly prepared compounds **5**, **6** and **8**, including benzothiazol-2-yl analogues of *sulofenur*, were screened *in vitro* for their potential cytotoxic activity using human urinary bladder cancer 5637, small cell lung cancer A-427 and large cell lung cancer LCLC-103H cell lines. None of these compounds exhibited cytotoxic activity at concentrations below 20 μM .

Scheme 2. Synthesis of compounds 3-6.

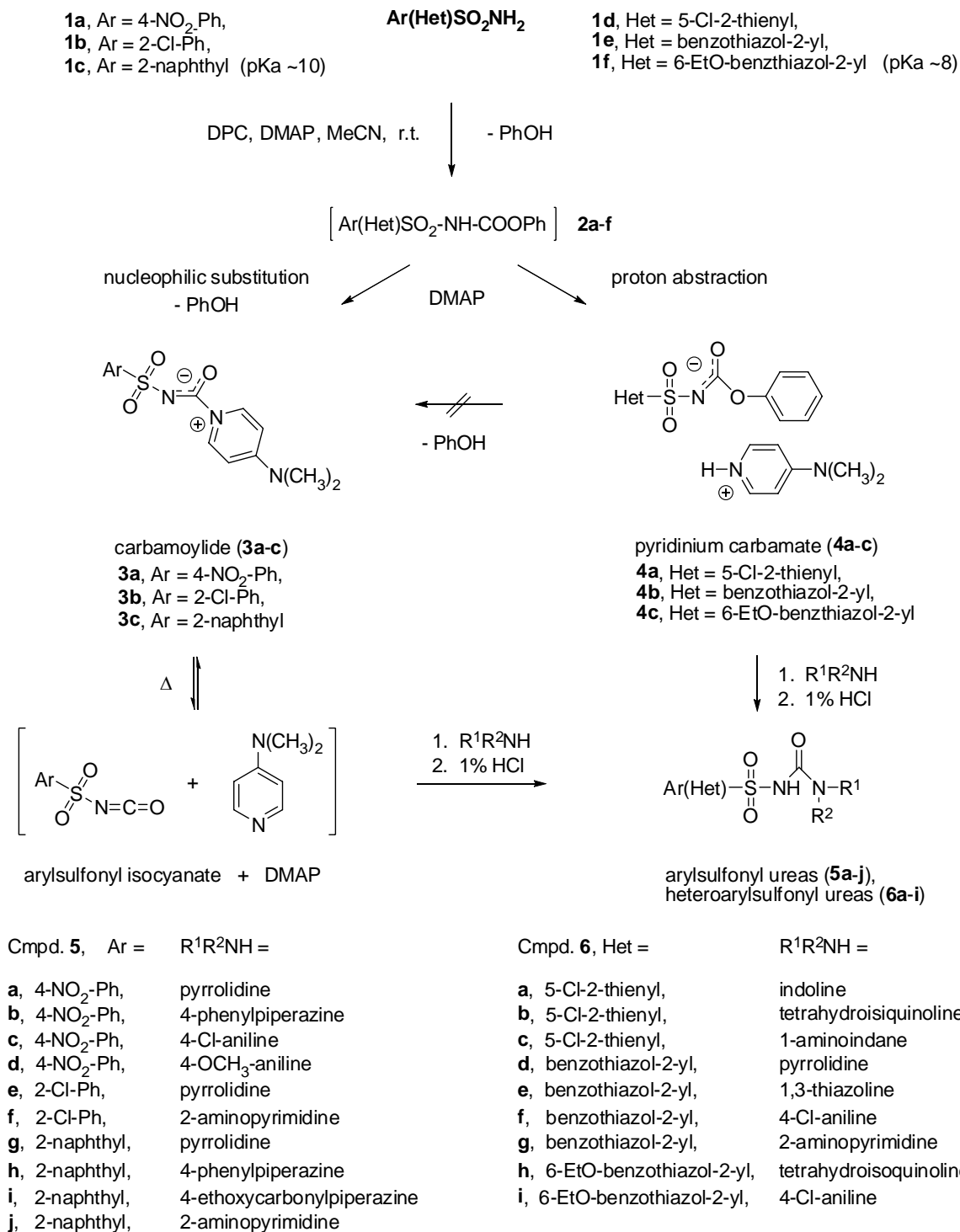
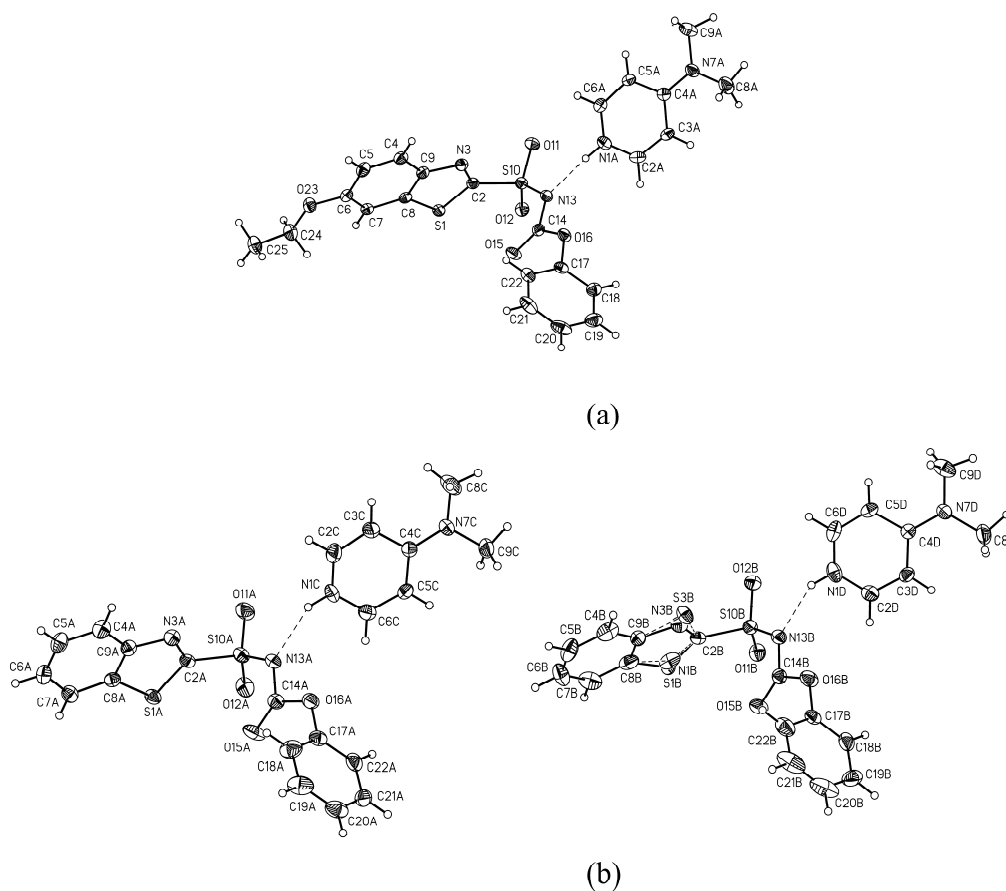
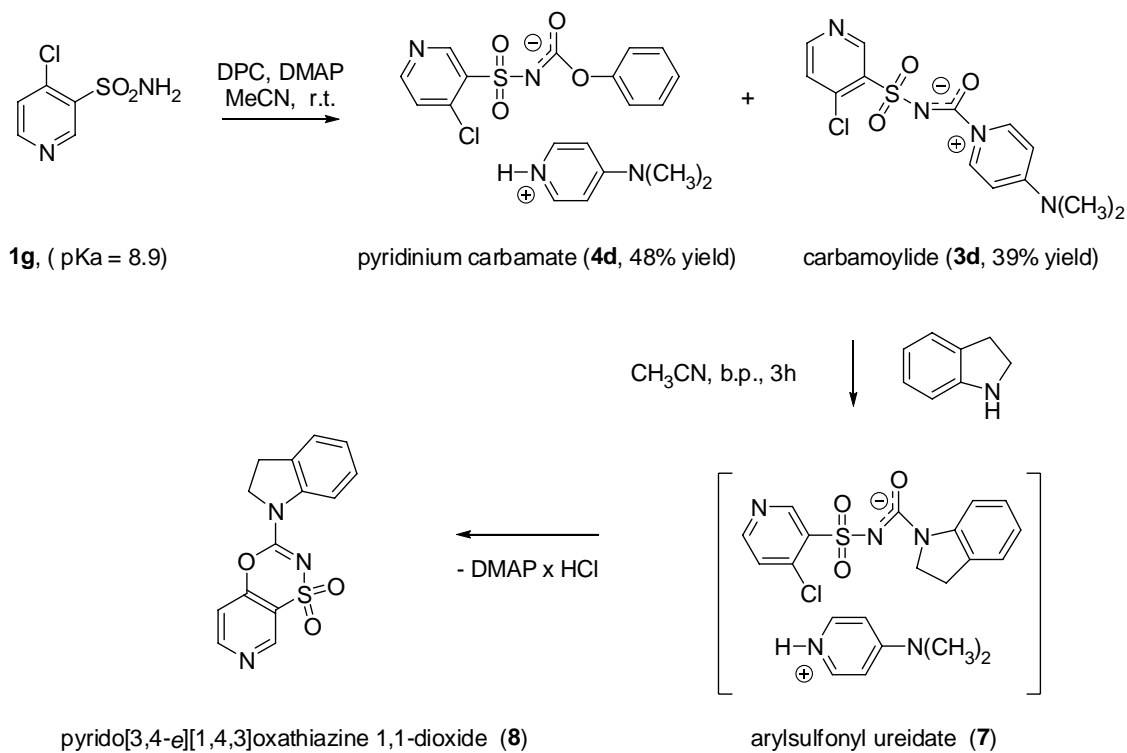


Figure 1. ORTEP drawings of (a) **4c** and (b) two symmetry independent molecules of **4b** with the atom labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.



Scheme 3. Synthesis of compound **8**.



3. Experimental

3.1. General

Melting points were measured on a Boetius 545 apparatus and are not corrected. The IR spectra were obtained on a Nicolet 380 FTIR spectrometer using potassium bromide pellets and the frequencies were quoted in cm^{-1} . The $^1\text{H-NMR}$ spectra were recorded on a Varian Gemini spectrometer at 200 MHz or a Varian Unity Plus apparatus at 500 MHz. The chemical shifts (δ) are expressed in ppm in relation to tetramethylsilane as a standard and the coupling constants (J) are given in Hz. The starting substrates were commercial reagents.

3.2. General procedure for the preparation of 4-dimethylaminopyridinium arylsulfonyl carbamoylides **3a-c** and 4-dimethylaminopyridinium heteroarylsulfonyl carbamates **4a-d**

A solution of appropriate arylsulfonamide **1a-c** (33 mmol) in acetonitrile (40 mL) was treated with 4-dimethylaminopyridine (DMAP, 4.1 g, 66 mmol) and the reaction mixture was stirred at room temperature until sulfonamide **1** had dissolved. Then diphenyl carbonate (DPC, 2.3 g, 37 mmol) was added and the reaction mixture was left overnight at room temperature. The solid that precipitated was separated by suction, washed with dry acetonitrile and dried to give pure carbamoylides **3a-d** or carbamates **4a-d**.

According to the above procedure the following compounds were obtained:

4-Dimethylaminopyridinium 4-nitrophenylsulfonyl carbamoylide (3a). Yield 56%; m.p. 175–177 °C (dec); IR (KBr) $\nu = 3099, 2937, 2683, 1691, 1645, 1578, 1520, 1349, 1294, 1257, 1215, 1159, 1072, 1078 \text{ cm}^{-1}$; $^1\text{H-NMR}$ (DMSO- d_6) $\delta = 3.33$ (s, 6H, CH_3), 6.97 (d, 2H, CH, $J = 7.2$ Hz), 8.31 (d, 2H, CH, $J = 8.7$ Hz), 8.71 (d, 2H, CH, $J = 8.7$ Hz), 8.95 (d, 2H, CH, $J = 7.2$ Hz); Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_5\text{S}$ (350.35) C, 47.99%; H, 4.03%; N, 15.99%; Found C, 47.72%; H, 3.87%; N, 15.83%.

4-Dimethylaminopyridinium 2-chlorophenylsulfonyl carbamoylide (3b). Yield: 54%; m.p. 112–115 °C; IR (KBr) $\nu = 3072, 2924, 1697, 1644, 1560, 1293, 1255, 1215, 1184, 1150, 1128, 1110, 1028 \text{ cm}^{-1}$; $^1\text{H-NMR}$ (DMSO- d_6) $\delta = 3.16$ (s, 6H, CH_3), 6.96 (d, 2H, CH, $J = 7.6$ Hz), 7.60 (d, 1H, CH), 7.20–7.47 (m, 2H, CH), 7.95 (d, 1H, CH), 8.65 (d, 2H, CH, $J = 7.6$ Hz); Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{ClN}_3\text{O}_3\text{S}$ (339.80) C, 49.49%; H, 4.15%; N, 12.37%; Found C, 49.18%; H, 4.29%; N, 12.31%.

4-Dimethylaminopyridinium naphth-2-ylsulfonyl carbamoylide (3c). Yield: 53%; m.p. 153–156 °C (dec); IR (KBr) $\nu = 3087, 1707, 1648, 1572, 1289, 1253, 1217, 1150, 1090, 1065, 862, 834, 768 \text{ cm}^{-1}$; $^1\text{H-NMR}$ (DMSO- d_6) $\delta = 3.22$ (s, 6H, CH_3), 6.95 (d, 2H, CH, $J = 7.3$ Hz), 7.60–7.69 (m, 2H, CH), 7.88–8.14 (m, 4H, CH), 8.43 (s, 1H, CH), 8.74 (d, 2H, CH, $J = 7.3$ Hz); Anal. Calcd. for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_3\text{S}$ (355.41) C, 60.83%; H, 4.82%; N, 11.82%; Found C, 60.58%; H, 4.77%; N, 11.59%.

4-Dimethylaminopyridinium (4-chloropyridin-3-ylsulfonyl carbamoyl)ide (3d). Yield: 39%; m.p. 151–153 °C (dec); IR (KBr) ν = 3097, 2934, 1702, 1645, 1572, 1559, 1449, 1395, 1296, 1260, 1089, 842, 824, 766, 596 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 3.25 (s, 6H, CH₃), 7.00 (d, 2H, CH, J = 8.1 Hz), 7.64 (d, 1H, CH, J = 5.2 Hz), 8.64 (d, 1H, CH, J = 5.2 Hz), 8.73 (d, 2H, CH, J = 8.1 Hz), 9.07 (s, 1H, CH); Anal. Calcd. for C₁₃H₁₃ClN₄O₃S (340.79) C, 45.82%; H, 3.85%; N, 16.44%; Found C, 45.61%; H, 3.90%; N, 16.16%.

4-(Dimethylamino)pyridinium (5-chlorothiophen-2-ylsulfonyl)(phenoxycarbonyl)amide (4a). Yield: 54%; m.p. 144–146 °C (dec); IR (KBr) ν = 3077, 2924, 2611, 1964, 1645, 1562, 1409, 1295, 1262, 1210, 1186, 1173, 1024, 988, 924, 887, 807, 626 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 3.18 (s, 6H, CH₃), 6.96–7.38 (m, 8H, CH), 7.42 (d, 1H, CH, J = 3.9 Hz), 8.21 (d, 2H, CH, J = 7.6 Hz), 12.6 (bs, 1H, NH); Anal. Calcd. for C₁₈H₁₈ClN₃O₄S₂ (439.94) C, 49.14%; H, 4.12%; N, 9.55%; Found C, 48.93%; H, 4.26%; N, 9.19%.

4-(Dimethylamino)pyridinium (benzothiazol-2-ylsulfonyl)(phenoxycarbonyl)amide (4b). Yield: 73%; m.p. 135–138 °C (dec); IR (KBr) ν = 3060, 2924, 1685, 1646, 1559, 1271 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 3.14 (s, 6H, CH₃), 6.92–6.96 (m, 4H, CH), 7.02–7.12 (t, 1H, J = 7.4 Hz), 7.25–7.32 (t, 2H, CH, J = 7.4 Hz), 7.45–7.62 (m, 2H, CH), 8.04–8.16 (m, 2H, CH), 8.29 (d, 2H, CH, J = 7.6 Hz); Anal. Calcd. for C₂₁H₂₀N₄O₄S₂ (456.54) C, 55.25%; H, 4.42%; N, 12.27%; Found C, 55.21%; H, 4.62%; N, 11.92%. Upon treatment of the above pyridinium salt with aqueous 1% HCl at room temperature the free carbamate **4b'** was obtained; m.p. 206–208 °C; IR (KBr) ν = 3007, 2851, 2799, 1758, 1458, 1222, 1096, 922, 767, 634 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 6.75 (d, 2H, CH, J = 7.8 Hz), 7.16 (t, 1H, CH, J = 7.8 Hz), 7.35 (t, 2H, CH, J = 7.8 Hz), 7.60–7.72 (m, 2H, CH), 8.16–8.30 (m, 2H, CH), 8.35 (s, 1H, NH); Anal. Calcd. for C₁₄H₁₀N₂O₄S₂ (334.37) C, 50.29%; H, 3.01%; N, 8.38%; Found C, 50.22%; H, 3.32%; N, 8.61%.

4-(Dimethylamino)pyridinium (6-ethoxybenzothiazol-2-ylsulfonyl)(phenoxy-carbonyl)amide (4c). Yield: 29.7%; m.p. 251–255 °C; IR (KBr) ν = 3223, 3066, 2924, 1681, 1645, 1557, 1296 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 1.35 (t, 3H, CH₃, J = 8.1 Hz), 3.14 (s, 6H, CH₃), 4.09 (q, 2H, CH₂, J = 8.1 Hz), 6.92–6.96 (m, 4H, CH), 7.05–7.15 (dd, 1H, CH, J_{ortho} = 6.75, J_{meta} = 2.3 Hz), 7.22–7.30 (t, 2H, CH, J = 7.4 Hz), 7.65 (d, 1H, CH, J_{meta} = 2.3 Hz), 7.93 (d, 1H, CH, J_{ortho} = 6.75 Hz), 8.19 (d, 2H, CH, J = 7.7 Hz); Anal. Calcd. for C₂₃H₂₄N₄O₅S₂ (500.59) C, 55.18%; H, 4.83%; N, 11.19%; Found C, 54.97%; H, 5.11%; N, 10.98%. Upon treatment of the above pyridinium salt with aqueous 1% HCl the free carbamate **4c'** was obtained; m.p. 206–208 °C; IR (KBr) ν = 2989, 2859, 2787, 2663, 1756, 1599, 1485, 1375, 1262, 1217, 1168, 1080, 1042, 842, 759, 688, 627 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 1.37 (t, 3H, CH₃, J = 8.2 Hz), 4.12 (q, 2H, CH₂, J = 8.2 Hz), 6.75 (m, 1H, CH), 7.00–7.45 (m, 5H, CH), 7.80–7.95 (m, 1H, CH), 8.00–8.15 (m, 1H, CH), 8.75 (bs, 1H, NH); Anal. Calcd. for C₁₆H₁₄N₂O₅S₂ (378.42) C, 50.78%; H, 3.73%; N, 7.40%; Found C, 50.53%; H, 3.89%; N, 7.06%.

4-(Dimethylamino)pyridinium (4-chloropyridin-3-ylsulfonyl)(phenoxycarbonyl)amide (4d). Yield: 48%; m.p. 191–193 °C; IR (KBr) ν = 3215, 3082, 2922, 1688, 1646, 1561, 1397, 1263, 1191, 1149, 1028, 916, 887, 806, 797 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 3.16 (s, 6H, CH₃), 6.88–6.93 (m, 2H, CH),

6.96 (d, 2H, CH, $J = 7.7$ Hz), 7.06 (t, 1H, CH, $J = 7.1$ Hz), 7.22-7.30 (m, 2H, CH), 7.56 (d, 1H, CH, $J = 5.3$ Hz), 8.20 (d, 2H, CH, $J = 7.7$ Hz), 8.53 (d, 1H, CH, $J = 5.3$ Hz), 8.96 (s, 1H, CH), 12.60 (bs, 1H, NH); Anal. Calcd. for $C_{19}H_{19}ClN_4O_4S$ (434.90) C, 52.47%; H, 4.40%; N, 12.88%; Found C, 52.19%; H, 4.71%; N, 12.60%.

3.3. General procedure for preparation of arylsulfonyl ureas **5** and heteroarylsulfonyl ureas **6**.

Reaction of carbamoylides **3a-c** and carbamates **4a-c** with aliphatic and aromatic amines

A mixture of carbamoylide **3** or carbamate **4** (2.8 mmol) and appropriate aliphatic or aromatic amine (3 mmol) in acetonitrile (10 mL) was heated at reflux for 10 min (in case of aliphatic) or 1 h (in case of aromatic) amine. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure to dryness. The oily residue was suspended in methanol and treated with 10% aqueous hydrochloric acid. The sulphonylureas **5** or **6** that precipitated were separated by suction, washed with methanol and water and re-crystallized from suitable solvent.

According to the above procedure the following sulphonylureas were obtained:

N-(4-Nitrophenylsulfonyl)pyrrolidine-1-carboxamide (**5a**). Yield: 17%; m.p. 187–193 °C (methanol); IR (KBr) $\nu = 3466, 3271, 3109, 2990, 2788, 1670, 1529, 1348, 1313, 1167, 1091, 1067$ cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) $\delta = 1.60$ -1.90 (m, 4H, CH_2CH_2), 3.15-3.45 (m, 4H, N- CH_2), 8.15 (d, 2H, CH, $J = 5.2$ Hz), 8.42 (d, 2H, CH, $J = 5.2$ Hz), 11.05 (bs, 1H, NH); Anal. Calcd. for $C_{11}H_{13}N_3O_5S$ (299.30) C, 44.14%; H, 4.38%; N, 14.04%; Found C, 44.08%; H, 4.52%; N, 13.96%.

N-(4-Nitrophenylsulfonyl)-4-phenylpiperazine-1-carboxamide (**5b**). Yield: 31%; m.p. 105–107 °C (ethanol); IR (KBr) $\nu = 3419, 3105, 2882, 1669, 1600, 1529, 1494, 1350, 1235, 1166, 1091$ cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) $\delta = 2.90$ -3.20 (m, 4H, CH_2), 3.30-3.60 (m, 4H, CH_2), 6.80 (t, 1H, CH, $J = 7.4$ Hz), 6.90 (d, 2H, CH, $J = 7.4$ Hz), 7.20 (t, 2H, CH, $J = 7.4$ Hz), 8.50 (d, 2H, CH, $J = 9.7$ Hz), 8.43 (d, 2H, CH, $J = 9.7$ Hz), 11.45 (bs, 1H, NH); Anal. Calcd. for $C_{17}H_{18}N_4O_5S$ (390.41) C, 52.30%; H, 4.65%; N, 14.35%; Found C, 52.05%; H, 4.83%; N, 14.16%.

N-(4-Chlorophenylcarbamoyl)-4-nitrophenylsulfonamide (**5c**). Yield: 42%; m.p. 165–170 °C (ethanol); IR (KBr) $\nu = 3438, 3351, 3112, 2890, 1715, 1607, 1542, 1351, 1158, 1086, 1039, 1013$ cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) $\delta = 7.32$ (d, 2H, CH, $J = 8.8$ Hz), 7.38 (d, 2H, CH, $J = 8.8$ Hz), 8.22 (d, 2H, CH, $J = 8.8$ Hz), 8.46 (d, 2H, CH, $J = 8.8$ Hz), 9.80 (bs, 1H, NH), 11.20 (bs, 1H, NH); Anal. Calcd. for $C_{13}H_{10}ClN_3O_5S$ (355.75) C, 43.89%; H, 2.83%; N, 11.81%; Found C, 44.17%; H, 3.12%; N, 11.57%.

N-(4-Methoxyphenylcarbamoyl)-4-nitrophenylsulfonamide (**5d**). Yield: 46%; m.p. 148–152 °C (ethanol); IR (KBr) $\nu = 3482, 3316, 3117, 3071, 3013, 2959, 2836, 1698, 1530, 1514, 1436, 1348, 1311, 1252, 1163, 1089, 1023$ cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) $\delta = 3.68$ (s, 3H, OCH_3), 6.84 (d, 2H, CH, $J = 9$ Hz), 7.24 (d, 2H, CH, $J = 9$ Hz), 8.20 (d, 2H, CH, $J = 9$ Hz), 8.45 (d, 2H, CH, $J = 9$ Hz); 8.93 (bs, 1H, NH), 11.2 (bs, 1H, NH); Anal. Calcd. for $C_{14}H_{13}N_3O_6S$ (351.33) C, 47.86%; H, 3.73%; N, 11.96%; Found C, 47.74%; H, 3.95%; N, 11.71%.

N-(2-Chlorophenylsulfonyl)pyrrolidine-1-carboxamide (**5e**). Yield: 37%; m.p. 175–190 °C (methanol); IR (KBr) ν = 3400, 3271, 3102, 3068, 1694, 1575, 1487, 1436, 1255, 1236, 1185, 1168, 1132, 1115 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 1.64-1.94 (m, 4H, CH_2), 3.15-4.5 (m, 4H, N- CH_2), 7.54-7.58 (m, 1H, CH), 7.60-7.68 (m, 2H, CH), 8.03 (d, 1H, CH, J = 7.7 Hz), 11.06 (s, 1H, NH); Anal. Calcd. for $\text{C}_{11}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S}$ (288.75) C, 45.75%; H, 4.54%; N, 9.70%; Found C, 45.61%; H, 4.82%; N, 9.47%.

2-Chloro-*N*-(pyrimidin-2-ylcarbamoyl)benzenesulfonamide (**5f**). Yield: 68%; m.p. 178–182 °C; IR (KBr) ν = 3148, 3067, 2970, 2920, 1715, 1582, 1470, 1449, 1402, 1353, 1282, 1155, 1130, 1075, 1006, 914, 866, 812 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 7.42-7.50 (m, 1H, CH), 7.65-7.80 (m, 3H, CH), 7.97-8.03 (d, 1H, CH, J = 7.6 Hz), 8.70-8.77 (m, 2H, CH), 10.69 (s, 1H, NH), 12.63 (bs, 1H, NH); Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{ClN}_4\text{O}_3\text{S}$ (312.73); C, 42.25%; H, 2.90%; N, 17.92%; Found C, 41.89%; H, 3.27%; N, 17.65%.

N-(Naphthalene-2-ylsulfonyl)pyrrolidine-1-carboxamide (**5g**). Yield: 48%; m.p. 203–208 °C (ethanol); IR (KBr) ν = 3266, 2975, 2870, 1692, 1441, 1328, 1157, 1057, 861, 748, 658 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 1.60-1.90 (m, 4H, CH_2), 3.15-3.45 (m, 4H, N- CH_2), 7.62-7.75 (m, 2H, CH), 7.91-8.21 (m, 4H, CH), 8.57 (s, 1H, CH), 10.77 (s, 1H, NH); Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$ (304.36) C, 59.19%; H, 5.30%; N, 9.20%; Found C, 58.98%; H, 5.43%; N, 9.01%.

N-(Naphthalene-2-ylsulfonyl)-4-phenylpiperazine-1-carboxamide (**5h**). Yield: 98%; m.p. 119–123 °C (ethanol); IR (KBr) ν = 3277, 3059, 3016, 2959, 2936, 1676, 1484, 1338, 1252, 1162, 1125, 1070, 1021, 876, 745 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 3.28-3.36 (m, 4H, CH_2), 3.66-3.74 (m, 4H, CH_2), 7.11-7.17 (m, 1H, CH), 7.30-7.40 (m, 4H, CH), 7.64-7.76 (m, 2H, CH), 7.92-8.22 (m, 4H, CH), 8.59 (s, 1H, CH), 11.35 (bs, 1H, NH); Anal. Calcd. for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$ (395.47) C, 63.78%; H, 5.35%; N, 10.63%; Found C, 63.56%; H, 5.50%; N, 10.33%.

Ethyl 4-(naphthalen-2-ylsulfonylcarbamoyl)piperazine-1-carboxylate (**5i**). Yield: 48%; m.p. 143–147 °C; IR (KBr) ν = 3196, 3060, 2978, 2930, 2868, 1709, 1677, 1469, 1441, 1257, 1230, 1163, 1072 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 1.16 (t, 3H, CH_3 , J = 7 Hz), 3.20-3.42 (m, 8H, CH_2), 4.02 (q, 2H, CH_2 , J = 7 Hz), 7.67-7.73 (m, 2H, CH), 7.88-7.93 (m, 1H, CH), 8.02-8.21 (m, 3H, CH), 8.55 (s, 1H, CH), 11.20 (bs, 1H, NH); Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_5\text{S}$ (391.44) C, 55.23%; H, 5.41%; N, 10.73%; Found C, 54.94%; H, 5.72%; N, 10.66%.

N-(Pyrimidin-2-ylcarbamoyl)naphthalene-2-sulfonamide (**5j**). Yield: 68%; m.p. 177–182 °C; IR (KBr) ν = 3148, 3067, 2971, 2920, 1716, 1583, 1471, 1449, 1354, 1283, 1156, 1075 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 7.20-7.24 (m, 1H, CH), 7.66-7.78 (m, 2H, CH), 7.98-8.26 (m, 4H, CH), 8.70-8.72 (m, 3H, CH), 10.70 (s, 1H, NH), 12.65 (bs, 1H, NH); Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{N}_4\text{O}_3\text{S}$ (328.35) C, 54.87%; H, 3.68%; N, 17.06%; Found C, 55.02%; H, 3.84%; N, 16.81%.

N-(5-Chlorothiophen-2-ylsulfonyl)indoline-1-carboxamide (**6a**). Yield: 73%; m.p. 182–184 °C; IR (KBr) ν = 3635, 3450, 2920, 1659, 1486, 1464, 1400, 1348, 1165, 1137, 1091, 998, 808, 871, 679, 620, 604 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 3.11 (t, 2H, CH_2 , J = 8.4 Hz), 4.03 (t, 2H, CH_2 , J = 8.4 Hz),

6.92-7.01 (m, 1H, CH), 7.08-7.23 (m, 2H, CH), 7.27 (d, 1H, CH, $J = 4.2$ Hz), 7.69 (d, 1H, CH, $J = 4.2$ Hz), 10.9 (bs, 1H, NH); Anal. Calcd. for $C_{13}H_{11}ClN_2O_3S_2$ (342.82) C, 45.55%; H, 3.23%; N, 8.17%; Found C, 45.38%; H, 3.59%; N, 7.93%.

N-(5-Chlorothiophen-2-ylsulfonyl)-3,4-dihydroisoquinoline-2(1H)-carboxamide (**6b**). Yield: 61%; m.p. 169–172 °C; IR (KBr) $\nu = 3107, 3020, 2896, 2805, 2751, 1646, 1481, 1410, 1344, 1235, 1167, 1001, 757, 616, 572$ cm^{-1} ; 1H -NMR (DMSO- d_6) $\delta = 2.81$ -2.82 (m, 2H, CH₂), 3.59-3.61 (m, 2H, CH₂), 4.53 (s, 2H, CH₂), 7.16-7.20 (m, 4H, CH), 7.25 (d, 1H, CH, $J = 3.9$ Hz), 7.64 (d, 1H, CH, $J = 3.9$ Hz), 11.44 (bs, 1H, NH); Anal. Calcd. for $C_{14}H_{13}ClN_2O_3S_2$ (356.85) C, 47.12%; H, 3.67%; N, 7.85%; Found C, 46.84%; H, 3.73%; N, 7.57%.

5-Chloro-*N*-(2,3-dihydro-1H-inden-1-ylcarbamoyl)thiophene-2-sulfonamide (**6c**). Yield: 49%, m.p. 144–148 °C; IR (KBr) $\nu = 3353, 3094, 1687, 1650, 1541, 1466, 1409, 1367, 1168, 995, 752, 679$ cm^{-1} ; 1H -NMR (DMSO- d_6) $\delta = 1.71$ -1.86 (m, 1H, CH), 2.30-2.48 (m, 1H, CH), 2.68-2.96 (m, 2H, CH), 5.00-5.18 (m, 1H, CH, $J = 8.0$ Hz), 6.99 (d, 1H, NH, $J = 8.0$ Hz), 7.10-7.24 (m, 4H, CH), 7.29 (d, 1H, CH, $J = 4.1$ Hz), 7.65 (d, 1H, CH, $J = 4.1$ Hz), 10.90 (bs, 1H, NH); Anal. Calcd. for $C_{14}H_{13}ClN_2O_3S_2$ (356.85) C, 47.12%; H, 3.67%; N, 7.85%; Found C, 46.97%; H, 3.95%; N, 7.82%.

N-(Benzothiazol-2-ylsulfonyl)pyrrolidine-1-carboxamide (**6d**). Yield: 80%; m.p. 220–222 °C; IR (KBr) $\nu = 3277, 2877, 1690, 1454, 1168, 1056, 860, 765, 625$ cm^{-1} ; 1H -NMR (DMSO- d_6) $\delta = 1.60$ -1.95 (m, 4H, CH₂), 3.25-3.65 (m, 4H, CH₂), 7.61-7.73 (m, 2H, CH), 8.16-8.32 (m, 2H, CH), 11.80 (bs, 1H, NH); Anal. Calcd. for $C_{12}H_{13}N_3O_3S_2$ (311.38); C, 46.29%; H, 4.21%; N, 13.49%; Found C, 45.97%; H, 4.53%; N, 13.42%.

N-(Benzothiazol-2-ylsulfonyl)thiazolidine-1-carboxamide (**6e**). Yield: 79%; m.p. 240–241 °C; IR (KBr) $\nu = 3068, 2887, 2791, 1681, 1455, 1181, 1385, 1092, 859, 626$ cm^{-1} ; 1H -NMR (DMSO- d_6) $\delta = 2.98$ -3.04 (m, 2H, CH₂), 3.59-3.63 (m, 2H, CH₂), 4.42 (s, 2H, CH₂), 7.61-7.74 (m, 2H, CH), 8.16-8.22 (m, 1H, CH), 8.26-8.33 (m, 1H, CH), 11.20 (bs, 1H, NH); Anal. Calcd. for $C_{11}H_{11}N_3O_3S_3$ (329.42) C, 40.11%; H, 3.37%; N, 12.76%; Found C, 39.87%; H, 3.42%; N, 12.40%.

N-(4-Chlorophenylcarbamoyl)benzothiazole-2-sulfonamide (**6f**). Yield: 81%, m.p. 182–184 °C; IR (KBr) $\nu = 3281, 1709, 1597, 1532, 1367, 1166, 1028, 923, 673$ cm^{-1} ; 1H -NMR (DMSO- d_6) $\delta = 7.28$ (d, 1H, CH, $J = 7.6$ Hz), 7.38 (d, 2H, CH, $J = 7.6$ Hz), 7.62-7.72 (m, 2H, CH), 8.16-8.23 (m, 1H, CH), 8.25-8.34 (m, 1H, CH), 9.39 (bs, 1H, NH), 12.6 (bs, 1H, NH); Anal. Calcd. for $C_{14}H_{10}ClN_3O_3S_2$ (367.83) C, 45.71%; H, 2.74%; N, 11.42%; Found C, 45.34%; H, 3.11%; N, 11.10%.

N-(Pyrimidin-2-ylcarbamoyl)benzothiazole-2-sulfonamide (**6g**). Yield: 70%; m.p. 312–314 °C; IR (KBr) $\nu = 3067, 2972, 2919, 1646, 1583, 1449, 1374, 1161, 1028, 917, 761$ cm^{-1} ; 1H -NMR (DMSO- d_6) $\delta = 7.27$ -7.32 (m, 1H, CH), 7.56-7.69 (m, 2H, CH), 8.10-8.16 (m, 1H, CH), 8.19-8.27 (m, 1H, CH), 8.73-8.76 (m, 2H, CH), 11.43 (bs, 2H, NH); Anal. Calcd. for $C_{12}H_9N_5O_3S_2$ (335.36) C, 42.98%; H, 2.70%; N, 20.88%; Found C, 42.71%; H, 3.02%; N, 20.57%.

N-(6-Ethoxybenzothiazol-2-ylsulfonyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (**6h**). Yield: 87%; m.p. 203–206 °C; IR (KBr) ν = 3145, 3088, 2956, 2876, 1648, 1555, 1432, 1386, 1145, 1128, 1034, cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 1.37 (t, 3H, CH₃, J = 7.8 Hz), 2.80 (t, 2H, CH₂, J = 6.8 Hz), 3.60 (t, 2H, CH₂, J = 6.8 Hz), 4.12 (q, 2H, CH₂, J = 7.8 Hz), 4.51 (s, 2H, CH₂), 7.05–7.2 (m, 4H, CH), 7.23 (dd, 1H, CH, J_{ortho} = 6.8 Hz, J_{meta} = 2.0 Hz), 7.80 (d, 1H, CH, J_{ortho} = 6.8 Hz), 8.05 (d, 1H, CH, J_{meta} = 2.0 Hz), 11.30 (bs, 1H, NH); Anal. Calcd. for C₁₉H₁₉N₃O₄S₂ (417.50) C, 54.66%; H, 4.59%; N, 10.06%; Found 54.56%; H, 4.85%; N, 10.03%.

N-(4-Chlorophenylcarbamoyl)-6-ethoxybenzothiazol-2-ylsulfonamide (**6i**). Yield: 75%; m.p. 238–240 °C; IR (KBr) ν = 3326, 3194, 3088, 2967, 2902, 2887, 1642, 1558, 1442, 1390, 1148, 1148, 1142, 1044 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 1.37 (t, 3H, CH₃, J = 7.7 Hz), 4.16 (q, 2H, CH₂, J = 7.7 Hz), 7.26 (dd, 1H, CH, J_{ortho} = 6.9 Hz, J_{meta} = 2.1 Hz), 7.30 (d, 2H, CH, J = 7.0 Hz), 7.38 (d, 2H, CH, J = 7.0 Hz), 7.80 (d, 1H, CH, J = 2.1 Hz), 8.06 (d, 1H, CH, J = 6.9 Hz), 9.30 (s, 1H, NH), 11.80 (bs, 1H, NH); Anal. Calcd. for C₁₆H₁₄ClN₃O₄S₂ (411.88) C, 46.66%; H, 3.43%; N, 10.20%; Found C, 46.73%; H, 3.68%; N, 9.83%.

3.4. Preparation of 3-(indolin-1-yl)-pyrido[3,4-*e*][1,4,3]oxathiazine 1,1-dioxide **8**

A mixture of carbamoylide **3d** or pyridinium carbamate **4d** (2.8 mmol) and indoline (3 mmol) in acetonitrile (10 mL) was heated at reflux for 3 h under reflux. The reaction mixture was cooled to room temperature and solvent was evaporated under reduced pressure to dryness. The crude residue triturated with methanol and water to give product **8** which was then separated by suction, washed with methanol and water and purified by crystallization from DMF. Yield: 33% and 29%, respectively; m.p. 248–250 °C; IR (KBr) ν = 2919, 1633, 1586, 1488, 1472, 1315, 1301, 1173, 1151, 1104, 1011, 765, 595 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 3.25 (t, 2H, CH₂, J = 7.8 Hz), 4.39 (t, 2H, CH₂, J = 7.8 Hz), 7.18–7.21 (m, 1H, CH), 7.34–7.39 (m, 2H, CH), 7.62 (d, 1H, CH, J = 5.4 Hz), 8.07–8.09 (m, 1H, CH), 8.88 (d, 1H, CH, J = 5.4 Hz), 9.13 (s, 1H, CH); Anal. Calcd. for C₁₄H₁₁N₃O₃S (301.32) C, 55.80%; H, 3.68%; N, 13.95%; Found C, 55.74%; H, 3.78%; N, 14.13%.

3.5. X-ray structure analysis

The diffraction data were collected with a KumaCCD diffractometer using graphite monochromated Mo K_{α} radiation. The intensity data were collected and processed using Oxford Diffraction CrysAlis Software [17]. The crystal structures were solved by direct methods with the program SHELXS-97 [18] and refined by full-matrix least-squares method on F^2 with SHELXL-97 [18].

*Crystal data for C₁₄H₉N₂O₄S₂·C₇H₁₁N₂ (**4b**):* Triclinic, space group *P*-1, a = 11.2168(5), b = 12.0651(6), c = 16.3837(8) Å, α = 79.042(4), β = 85.852(4), γ = 83.798(4)°, V = 2161.02(18) Å³, Z = 4, d_x = 1.403 g·cm⁻³, T = 130K. Data were collected for a crystal with dimensions 0.4x0.4x0.3 mm. Final R indices for 5697 reflections with $I > 2\sigma(I)$ and 582 refined parameters are: R_1 = 0.0319, wR_2 = 0.0764 (R_1 = 0.0490, wR_2 = 0.0864 for all 7589 data). The benzothiazole ring of one of the symmetry independent molecules is disordered over two strongly overlapping positions.

Crystal data for $C_{16}H_{13}N_2O_5S_2 \cdot C_7H_{11}N_2$ (**4c**): Monoclinic, space group $P2_1/n$, $a = 12.3446(2)$, $b = 12.5528(2)$, $c = 15.6694(3)$ Å, $\beta = 99.7467(18)^\circ$, $V = 2393.07(7)$ Å³, $Z = 4$, $d_x = 1.389$ g.cm⁻³, $T = 130$ K. Data were collected for a crystal with dimensions 0.5x0.5x0.1 mm. Final R indices for 4467 reflections with $I > 2\sigma(I)$ and 314 refined parameters are: $R_1 = 0.0291$, $wR_2 = 0.0721$ ($R_1 = 0.0391$, $wR_2 = 0.0832$ for all 5320 data).

Crystallographic data for compounds **4b** and **4c** have been deposited with Cambridge Crystallographic Data Centre (CCDC deposition numbers CCDC 742624-742625). Copies of the data can be obtained upon request from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, quoting the deposition numbers.

3.6. *In vitro* cytotoxicity assay

The following primary screening of the new compounds was done to indicate whether a substance possesses enough activity at the concentration of 20 µM to inhibit human tumor cell growth by 50% ($GI_{50} < 20$ µM).

The *in vitro* cytotoxic activity of all arylsulfonylureas **5a-j** and heteroarylsulfonylureas **6a-i** were evaluated [19,20] using human urinary bladder cancer 5637, small cell lung cancer A-427 and large cell lung cancer LCLC-103H cell lines. The assay was carried out in 96-well microtiter plates. When the cells were putted into the plates after 24 h cells were treated with appropriate drug solutions. The cytotoxic effects of the compounds were measured after a 96 h continuous exposure to the substances. The cell growth inhibition values were estimated by staining the adherent cells with crystal violet. Only viable cells remained attached to the plastic surface of the wells and bind the dye. The unbound dye was washed out with water and stain remaining in the wells was redissolved with 70% ethanol. Finally, the optical density (OD) was measured with a microplate reader set at $\lambda = 570$ nm.

4. Conclusions

The current work has addressed the use of environmentally non hazardous aryl(heteroaryl)sulfonamides and diphenyl carbonate (DPC) in the synthesis of 4-dimethylamino-pyridinium *N*-[aryl(heteroaryl)sulfonyl] carbamoylides of type **3**, the stable and easy-to-handle substitutes of aryl(heteroaryl)sulfonyl isocyanates. The comparison of the existing literature methods for the preparation of arylsulfonyl/heteroaryl carbamates and ureas from arylsulfonamides suggests that the DPC/DMAP approach is superior. Some of the advantages include mild reaction conditions, the ease of preparation and product separation and the extended shelf-life of the parent ylides. Moreover, a very high reactivity of pyridinium carbamoylides renders them suitable for the syntheses of arylsulfonyl ureas. It should be emphasized, however, that in the above procedure diphenyl carbonate (DPC) could not be replaced by the less reactive diethyl or dimethyl carbonates.

It has been also found that the course of the reaction between sulphonamide and DPC/DMAP couple depends on pK_a of the substrate. Thus, arylsulphonamides with pK_a in the range of 9-10 give the desired carbamoylides **3**, while the more acidic heteroarylsulfonamides ($pK_a \sim 8$) react preferentially with the formation of pyridinium salts of the intermediary formed carbamates **4**.

Although none of the compounds described in this work exhibited pronounced cytotoxic activity against selected human tumor cell lines, yet the biological potential of these derivatives incorporating aryl(heteroaryl)sulfonylurea pharmacophoric group presented in Introduction remains to be explored.

References and Notes

1. Gribble, F.M.; Reimann, F. Differential selectivity of insulin secretagogues: Mechanisms, clinical implications, and drug interactions. *J. Diabetes Complicat.* **2003**, *2*, 11–15.
2. Knauf, H.; Mutschler, E. Clinical Pharmacokinetics and Pharmacodynamics of Torasemide. *Clin. Pharmacokinet.* **1998**, *34*, 1–24.
3. Rolin, S.; Hanson, J.; Vastersaegher, C.; Cherdon, C.; Pratico, D.; Masereel, B.; Dogne, J.-M. BM-520, an original TXA₂ modulator, inhibits the action of thromboxane A₂ and 8-iso-prostaglandin F_{2α} *in vitro* and *in vivo* on human and rodent platelets, and aortic vascular smooth muscles from rodents. *Prostagland. Other Lipid Mediat.* **2007**, *84*, 14–23.
4. De Leval, X.; Dassesse, T.; Dogne, J.-M.; Waltregny, D.; Bellahcene, A.; Benoit, V.; Pirotte, B.; Castronovo, V. Evaluation of original dual thromboxane A₂ modulators as antiangiogenic agents. *J. Pharmacol. Exp. Ther.* **2006**, *318*, 1057–1067.
5. Guo, W.-C.; Liu, X.-H.; Li, Y.-H.; Wang, S.-H.; Li, Z.-M. Synthesis and Herbicidal Activity of Novel Sulfonylureas Containing Thiadiazol Moiety. *Chem. Res. Chin. Univ.* **2008**, *24*, 32–35.
6. Sohn, H.; Lee, K.-S.; Ko, Y.-K.; Ryu, J.-W.; Woo, J.-C.; Koo, D.-W.; Shin, S.-J.; Ahn, S.-J.; Shin, A.-R.; Song, C.-H.; Jo, E.-K.; Park, J.-K.; Kim, H.-J. *In vitro* and *ex vivo* activity of new derivatives of acetohydroxyacid synthase inhibitors against *Mycobacterium tuberculosis* and non-tuberculous mycobacteria. *Int. J. Antimicrob. Agents* **2008**, *31*, 567–571.
7. Cyrus, T.; Yao, Y.; Ding, T.; Dogne, J.-M.; Pratico, D. A novel thromboxane receptor antagonist and synthase inhibitor, BM-573, reduces development and progression of atherosclerosis in LDL receptor deficient mice. *Eur. J. Pharmacol.* **2007**, *561*, 105–111.
8. Li, R.; Chen, X.; Gong, B.; Dominguez, J.N.; Davidson, E.; Kurzban, G.; Miller, R.E.; Nuzum, E.O.; Rosenthal, P.J. *In vitro* antimalarial activity of chalcones and their derivatives. *J. Med. Chem.* **1995**, *38*, 5031–5037.
9. Mastrolorenzo, A.; Scozzafava, A.; Supuran, C.T. Antifungal activity of silver and zinc complexes of sulfadruug derivatives incorporating arylsulfonylureido moieties. *Eur. J. Pharm. Sci.* **2000**, *11*, 99–107.
10. Rostom, S.A.F. Synthesis and *in vitro* antitumor evaluation of some indeno[1,2-*c*]pyrazol(in)es substituted with sulfonamide, sulfonylurea(-thiourea) pharmacophores, and some derived thiazole ring systems. *Bioorg. Med. Chem.* **2006**, *14*, 6475–6485.
11. Winters, M.P.; Crysler, C.; Subasinghe, N.; Ryan, D.; Leong, L.; Zhao, S.; Donatelli, R.; Yurkow, E.; Mazzulla, M.; Boczon, L.; Manthey, C.L.; Molloy, C.; Raymond, H.; Murray, L.; McAlonan, L.; Tomczuk, B. Carboxylic acid bioisosteres acylsulfonamides, acylsulfamides, and sulfonylureas as novel antagonists of the CXCR2 receptor. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1926–1930.

12. Sączewski, F.; Kornicka, A.; Brzozowski, Z. 4-Dimethylaminopyridinium carbamoylides as stable and non-hazardous substitutes of arylsulfonyl and heteroaryl isocyanates. *Green Chem.* **2006**, *8*, 647–656.
13. Sączewski, J.; Gdaniec, M. The structure and theoretical study of 4-dimethylaminopyridinium *N*-(arylsulfonyl)carbamoylides. *J. Mol. Struct.* **2009**, *921*, 13–17.
14. Lewis, R.A.; Schoenwald, R.D.; Eller M.G.; Barfknecht, C.F.; Phelps, C.D. Ethozolamide Analogue Gel. *Arch. Ophthalmol.* **1984**, *102*, 1821–1824.
15. Krishnamurthy, V.M.; Bohall, B.R.; Kim, C.-Y.; Moustakas, D.T.; Christianson, D.W.; Whitesides, G.M. Thermodynamic parameters for association of fluorinated benzenesulfonamides with bovine carbonic anhydrase II. *Chem. Asian J.* **2007**, *2*, 94–105.
16. The pK_a value was determined at 25 °C by potentiometric titration with TiNet 2.5 software.
17. *Oxford Diffraction, CrysAlis CCD and RED, ver. 1.173*. Oxford Diffraction: Oxfordshire, UK, 2007.
18. Sheldrick, G.M. A short history of SHELX. *Acta Crystallogr. A* **2008**, *64*, 112–122.
19. Bracht, K.; Boubakari; Grünert, R.; Bednarski, P.J. Correlations between the activities of 19 anti-tumor agents and the intracellular glutathione concentrations in a panel of 14 human cancer cell lines: Comparisons with the National Cancer Institute data. *Anticancer Drugs* **2006**, *17*, 41–51.
20. Rinke, K.; Grünert, R.; Bednarski, P.J. New synthetic route to [bis-1,2-(aminomethyl)benzene]dichloroplatinum(II) complexes, screening for cytotoxic activity in cisplatin-sensitive and resistant human cancer cell lines, and reaction with glutathione. *Pharmazie* **2001**, *56*, 763–769.

Sample Availability: Samples of the compounds **3**, **4** and **8** are available from the authors.

© 2010 by the authors; licensee Molecular Diversity Preservation International, Basel, Switzerland. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/3.0/>).