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Syntheses of 1-(Phenylsulfonyl)-(1*H*,3*H*)-imidazol-2-one Derivatives with Potential Biological Activity

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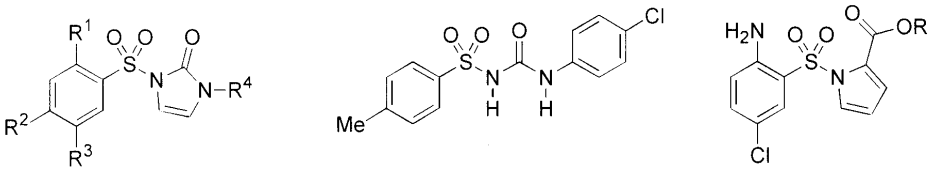
A series of 1-(arylsulfonyl)-3-(2,2-dimethoxyethyl)ureas (**2a–e**) was obtained by the reaction of 1-(phenylsulfonyl)ureas (**1a–e**) with aminoacetaldehyde dimethyl acetal in boiling dioxane. Cyclocondensation reactions of the 1-(arylsulfonyl)-3-(2,2-dimethoxyethyl)ureas (**2a–e**) in 98% H_2SO_4 gave the appropriate 1-(arylsulfonyl)-(1*H*,3*H*)-imidazol-2-ones (**3a–e**) in good yields. The subsequent reaction of **3a** with methanesulfonyl- or 4-nitrophenylsulfonyl chlorides furnished the 3-(R^4-sulfonyl) derivatives **4** and **5**, respectively. Preliminary screening data indicated that the compounds **3c–e, 4** and **5** were inactive against three selected human tumor cell lines derived from Breast cancer (MCF7), Lung cancer (NCI-H460) and CNS cancer (SF-268).

Key words: 1-(phenylsulfonyl)-(1*H*,3*H*)-imidazol-2-ones, synthesis, antitumor effect

The arylsulfonamides constitute an important class of compounds with several types of biological activities and well-established safety profile. A large number of structurally novel sulfonamide derivatives have been reported to possess substantial antitumor [1–11] and antiviral [2,3,12] activity. Continuing the studies on development of novel arylsulfonamides possessing such activities [6–12], in the present work we report the synthesis and preliminary biological evaluation of the title compounds of type **I** (Figure 1) as structural analogues of antitumor active diarylsulfonylureas [13] (**II**, Figure 1), and pyrrolyl aryl sulfones [14] (**III**, Figure 1) with pronounced anti-HIV-1 activity.



I II (LY 181984) III

Figure 1.

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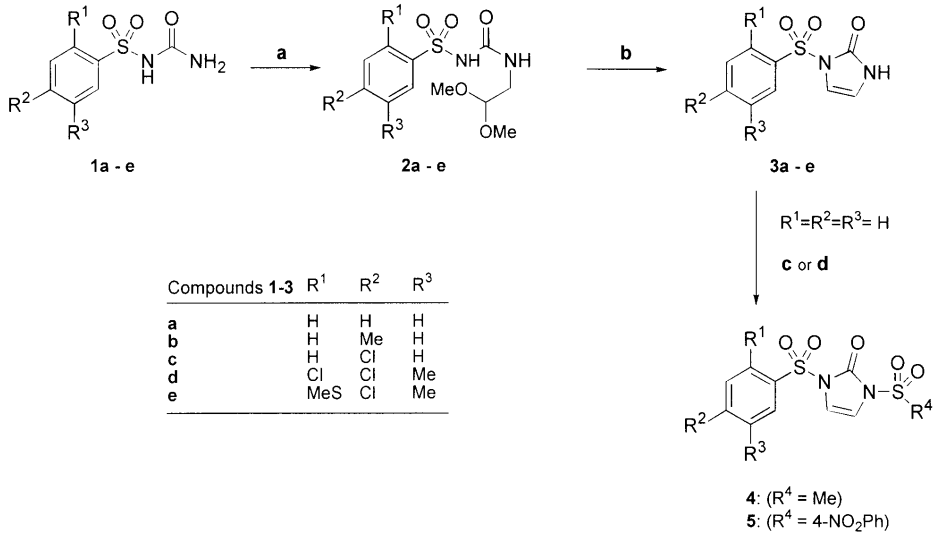
RESULTS AND DISCUSSION

The syntheses of the target compounds **3a–e** were achieved by a convenient two step procedure starting from 1-(phenylsulfonyl)ureas **1a–e** as shown in Scheme 1.



Compounds **1-3**	R^1	R^2	R^3
a	H	H	H
b	H	Me	H
c	H	Cl	H
d	Cl	Cl	Me
e	MeS	Cl	Me

Scheme 1. Reagents, conditions and yields: (**a**) $H_2NCH_2CH(OMe)_2$, dry dioxane, reflux 3–40 h, 76–82%; (**b**) 98% H_2SO_4, 20–40°C, 0.5 h and 20°C, 10–12 h, 67–97%; (**c**) $MeSO_2Cl$ (1.2 molar equiv.), TEA, CH_2Cl_2, reflux, 1 h, 75%; (**d**) 4-NO_2PhSO_2Cl, pyridine, 20°C, 3 h, 81%.

First, the reaction of **1a–e** with aminoacetaldehyde dimethyl acetal carried out in dry dioxane at elevated temperature led to the formation of 1-(arylsulfonyl)-3-(2,2-dimethoxyethyl)ureas **2a–e**, which could be separated in good yields (76–82%). Then, upon treatment of **2a–e** with an excess of 98% H_2SO_4 at room temperature the desired 1-(arylsulfonyl)-(1*H*,3*H*)-imidazol-2-ones **3a–e** were obtained, either in high yields (95–97%) for **3c** and **3d** or in good yields (67–86%) for **3a,b,e**. The subsequent reactions of **3a** with methanesulfonyl chloride in the presence of triethylamine in methylene chloride or with 4-nitrophenylsulfonyl chloride in pyridine afforded the expected 1,3-disubstituted (1*H*,3*H*)-imidazol-2-ones **4** and **5** (Scheme 1), respectively.

The anticancer activity of compounds **3a–e**, **4** and **5** was evaluated *in vitro*, using primary anticancer assay at concentration of 0.1 mM in the 3-cell line panel consisting of the MCF7 (Breast), NCI-H460 (Lung) and SF-268 (CNS) at the US National Cancer Institute (Bethesda, MD). However, the tumor cell growth inhibition data indicated that all compounds were inactive ($GI_{50} > 100\,\mu M$). It is pertinent to note that, further evaluations concerning antiviral activity of arylsulfonyl imidazolone derivatives of type **I** are in progress.

EXPERIMENTAL

Melting points were determined on a Bűchi SMP 20 apparatus and were uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer FT IR 1600 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini (200 MHz) spectrometer using TMS as internal standard (δ values in ppm). Thin-layer chromatography was performed on Merck Kieselgel 60F_{254} plates and visualised with UV or with iodine vapour. The starting 1-(phenylsulfonyl)ureas **1a–c** were synthesized according to the procedure described in [15].

1-(Arylsulfonyl)-3-(2,2-dimethoxyethyl)ureas (2a–e). General procedure. A mixture of the appropriate 1-(phenylsulfonyl)urea (**1a–e**) (30 mmol), aminoacetaldehyde dimethyl acetal (3.4 g, 32 mmol) and dry dioxane (40 ml for **1a–c** or 90 ml for **1d** and **1e**) was refluxed until the evolution of NH_3 had ceased (30–40 h). The reaction mixture was evaporated under reduced pressure to dryness. The solid residue was dissolved in 2% aqueous NaOH solution (75 ml, 20°C) then neutralized to pH = 7 with 1% hydrochloric acid. After 2 h of stirring the small amount of insoluble side product was filtered off together with charcoal added. The clear filtrate was acidified to pH 4 with 0.5% hydrochloric acid. The product that precipitated was collected by filtration, washed with water, and dried initially at room temperature and then at 60°C.

In this manner, the following ureas were obtained.

1-(Phenylsulfonyl)-3-(2,2-dimethoxyethyl)urea (2a). Yield 7.1 g, 82%, (white prisms), m.p. 80–81°C. IR (KBr) cm^{-1}: 3345, 3260, 1690, 1330, 1165. ^{1}H NMR ($CDCl_3$) δ: 3.36 (t, 2H, NHC$\underline{H}_2$CH), 3.38 (s, 6H, OCH_3), 4.35 (t, 1H, CH), 6.76 (t, 1H, N$\underline{H}CH_2$), 7.47–7.67 (m, 3H, aromatic), 7.91–7.95 (m, 2H, aromatic), 9.10 (s, 1H, SO_2NH). ^{13}C NMR ($CDCl_3$) δ: 40.94, 53.76, 101.65, 126.44, 128.55, 133.00, 138.90, 151.39. Anal. Calcd. for $C_{11}H_{16}N_2O_5S$: C, 45.8; H, 5.6; N, 9.7. Found: C, 45.7; H, 5.8; N, 9.8.

1-(4-Methylphenylsulfonyl)-3-(2,2-dimethoxyethyl)urea (2b). Yield 7.3 g, 80%, (white crystals), m.p. 92–93°C. IR (KBr) cm^{-1}: 3375, 3135, 1690, 1345, 1155. ^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 3H, CH_3-Ar), 3.36 (t, 2H, NHC$\underline{H}_2$CH), 3.38 (s, 6H, OCH_3), 4.36 (t, 1H, CH), 6.67 (t, 1H, N$\underline{H}CH_2$), 7.32 (d, J = 8.2 Hz, 2H, aromatic), 7.81 (d, J = 8.2 Hz, 2H, aromatic), 8.88 (s, 1H, SO_2NH). ^{13}C NMR ($CDCl_3$) δ: 21.57, 41.56, 54.34, 102.29, 127.10, 129.77, 136.58, 144.67, 151.96. Anal. Calcd. for $C_{12}H_{18}N_2O_5S$: C, 47.7; H, 6.0; N, 9.3. Found: C, 47.6; H, 6.2; N, 9.3.

1-(4-Chlorophenylsulfonyl)-3-(2,2-dimethoxyethyl)urea (2c). Yield 7.8 g, 80%, (white prisms), m.p. 92–93°C. IR (KBr) cm^{-1}: 3310, 3225, 1690, 1345, 1175. ^{1}H NMR ($CDCl_3$) δ: 3.34 (t, 2H, NHC$\underline{H}_2$CH), 3.37 (s, 6H, OCH_3), 4.36 (t, 1H, CH), 6.71 (t, 1H, N$\underline{H}CH_2$), 7.50 (d, J = 8.75 Hz, 2H, aromatic), 7.88 (d, J = 8.75 Hz, 2H, aromatic), 9.02 (s, 1H, SO_2NH). Anal. Calcd. for $C_{11}H_{15}ClN_2O_5S$: C, 40.9; H, 4.7; N, 8.7. Found: C, 40.8; H, 4.8; N, 8.8.

1-(2,4-Dichloro-5-methylphenylsulfonyl)-3-(2,2-dimethoxyethyl)urea (2d). Yield 8.8 g, 79%, (white prisms), m.p. 158–159°C. IR (KBr) cm^{-1}: 3320, 3170, 1655, 1360, 1170. ^{1}H NMR ($CDCl_3$) δ: 2.43 (s, 3H, CH_3-Ar), 3.33 (t, 2H, NHC$\underline{H}_2$CH), 3.36 (s, 6H, OCH_3), 4.32 (t, 1H, CH), 6.55 (t, 1H, N$\underline{H}CH_2$), 7.55 (s, 1H, H-3), 7.99 (s, 1H, H-6), 8.21 (s, 1H, SO_2NH). Anal. Calcd. for $C_{12}H_{16}Cl_2N_2O_5S$: C, 38.8; H, 4.3; N, 7.5. Found: C, 38.9; H, 4.6; N, 7.7.

1-(4-Chloro-5-methyl-2-methylthiophenylsulfonyl)-3-(2,2-dimethoxyethyl)urea (2e). Yield 8.8 g, 76%, (white crystals), m.p. 150–151°C. IR (KBr) cm^{-1}: 3340, 3255, 1660, 1350, 1160. ^{1}H NMR ($CDCl_3$) δ: 2.40 (s, 3H, CH_3-Ar), 2.56 (s, 3H, SCH_3), 3.31 (t, 2H, NHC$\underline{H}_2$CH), 3.35 (s, 6H, OCH_3), 4.32 (t, 1H, CH), 6.59 (t, 1H, N$\underline{H}CH_2$), 7.38 (s, 1H, H-3), 7.88 (s, 1H, H-6), 8.00 (s, 1H, SO_2NH). Anal. Calcd. for $C_{13}H_{19}ClN_2O_5S_2$: C, 40.8; H, 5.0; N, 7.3. Found: C, 40.6; H, 5.2; N, 7.4.

1-(Phenylsulfonyl)-(1*H*,3*H*)-imidazol-2-ones (3a–e). General procedure. A suitable 1-(arylsulfonyl)-3-(2,2-dimethoxyethyl)urea (**2a–e**) (15 mmol) was added as a solid in several portions to 98% sulfuric acid (17 ml). After an exothermic reaction had completed (40–45°C), the reaction mixture was left to stand at room temperature for 10–12 h. The resulting solution was poured into water-crushed ice mixture (250–300 g, 0–2°C) and stirred at room temperature for 1 h. The precipitate thus obtained was collected by filtration, washed thoroughly with water and diluted methanol (50%, 3× 5 ml), and dried initially at room temperature and then at 70°C.

In this manner, the following products were obtained.

1-(Phenylsulfonyl)-(1*H*,3*H*)-imidazol-2-one (3a). Yield 2.9 g, 86%, (white plates), m.p. 188–190°C. IR (KBr) cm^{-1}: 3150, 3110, 1715, 1680, 1370, 1175. ^{1}H NMR ($CDCl_3$) δ: 6.35 (t, 1H, H-4, imidazo.), 6.72 (t, 1H, H-5, imidazo.), 7.50–7.70 (m, 5H, aromatic), 10.03 (s, 1H NH). ^{13}C NMR ($CDCl_3$) δ: 109.27, 111.34, 127.93, 129.22, 134.46, 137.36, 151.95. Anal. Calcd. for $C_9H_8N_2O_3S$: C, 48.2; H, 3.6; N, 12.5. Found: C, 48.3; H, 3.7; N, 12.6.

1-(4-Methylphenylsulfonyl)-(1*H*,3*H*)-imidazol-2-one (3b). Yield 3.0 g, 84%, (white crystals), m.p. 172–174°C. IR (KBr) cm^{-1}: 3155, 3145, 1715, 1680, 1375, 1180. ^{1}H NMR ($CDCl_3$) δ: 2.34 (s, 3H, CH_3), 6.33 (t, 1H, H-4, imidazo.), 6.70 (t, 1H, H-5, imidazo.), 7.33 (d, J = 8.3 Hz, 2H, aromatic), 7.92 (d, J = 8.2 Hz, 2H, aromatic), 10.00 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 21.68, 109.30, 111.14, 128.00, 129.83, 134.32, 145.72, 151.95. Anal. Calcd. for $C_{10}H_{10}N_2O_3S$: C, 50.4; H, 4.2; N, 11.8. Found: C, 50.3; H, 4.4; N, 11.9.

1-(4-Chlorophenylsulfonyl)-(1*H*,3*H*)-imidazol-2-one (3c). Yield 3.7 g, 95%, (white crystals), m.p. 182–184°C. IR (KBr) cm^{-1}: 3155, 1720, 1685, 1370, 1180. ^{1}H NMR ($CDCl_3$) δ: 6.36 (t, 1H, H-4, imidazo.), 6.72 (t, 1H, H-5, imidazo.), 7.38 (d, J = 8.6 Hz, 2H, aromatic), 7.99 (d, J = 8.6 Hz, 2H, aromatic), 9.86 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 109.19, 111.35, 129.48, 129.55, 135.54, 141.36, 151.75. Anal. Calcd. for $C_9H_7ClN_2O_3S$: C, 41.8; H, 2.7; N, 10.8. Found: C, 41.9; H, 2.8; N, 10.9.

1-(2,4-Dichloro-5-methylphenylsulfonyl)-(1*H*,3*H*)-imidazol-2-one (3d). Yield 4.5 g, 97%, (white crystals), m.p. 215–216°C. IR (KBr) cm^{-1}: 3195, 3165, 1720, 1685, 1380, 1180. ^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 3H, CH_3), 6.33 (t, 1H, H-4, imidazo.), 7.50 (t, 1H, H-5, imidazo.), 7.51 (s, 1H, H-3, aromatic), 8.19 (s, 1H, H-6, aromatic), 9.40 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 19.67, 110.22, 111.04, 130.12, 131.91, 132.60, 134.80, 136.11, 141.69, 151,20. Anal. Calcd. for $C_{10}H_8Cl_2N_2O_3S$: C, 39.1; H, 2.6; N, 9.1. Found: C, 39.2; 2.7; N, 9.2.

1-(4-Chloro-5-methyl-2-methylthiophenylsulfonyl)-(1*H*,3*H*)-imidazol-2-one (3e). Yield 3.2 g, 67%, (white amorphous powder), m.p. 209–211°C. IR (KBr) cm^{-1}: 3200, 3140, 1715, 1685, 1370, 1170. ^{1}H NMR ($CDCl_3$) δ: 2.36 (s, 3H, CH_3-Ar), 3.48 (s, 3H, SCH_3), 6.63 (s, 1H, H-4, imidazo.), 6.85 (s, 1H, H-5, imidazo.), 7.46 (s, 1H, H-3, aromatic), 8.01 (s, 1H, H-6, aromatic), 10.52 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 15.17, 18.91, 110.14, 111.25, 126.43, 131.27, 131.86, 134.13, 138.81, 140.40, 149.81. Anal. Calcd. for $C_{11}H_{11}ClN_2O_3S_2$: C, 41.4; H, 3.5; N, 8.8. Found: C, 41.4; H, 3.6; N, 8.9.

3-(Methanesulfonyl)-1-(phenylsulfonyl)-(1*H*,3*H*)-imidazol-2-one (4). To a stirred suspension of **3a** (3.36 g, 15 mmol), in CH_2Cl_2 (15 ml) and TEA (2.0 g, 20 mmol) a solution of methanesulfonyl chloride (2.1 g, 18 mmol) in CH_2Cl_2 (10 ml) was added. After an exothermic reaction had completed (37–39°C), the reaction mixture was refluxed for 1 h. The sample was cooled down to room temperature and the precipitate was filtered off, washed successively with methanol (2× 2 ml) and water (50 ml), then dried. The crude reaction product was purified by crystallization from methylene chloride to afford **4** as white prisms (3.4 g, 75%, m.p. 151–152°C). IR (KBr) cm^{-1}: 2935, 1735, 1370, 1345, 1325, 1190, 1170, 1140. ^{1}H NMR (DMSO-d_6) δ: 3.53 (s, 2H, CH_3), 7.01 (d, J = 3.6 Hz, 1H, H-4, imidazo.), 7.20 (d, J = 3.6 Hz, 1H, H-5, imidazo.), 7.69–7.77 (m, 2H, aromatic), 7.82–7.86 (m, 1H, aromatic), 8.02–8.07 (m, 2H, aromatic). ^{13}C NMR (DMSO-d_6) δ: 58.20, 110.28, 110.93, 127.90, 129.93, 135.56, 135.94, 145.96. Anal. Calcd. for $C_{10}H_{10}N_2O_5S_2$: C, 39.7; H, 3.3; N, 9.3. Found: C, 39.9; H, 3.4; N, 9.4.

3-(4-Nitrophenylsulfonyl)-1-(phenylsulfonyl)-(1*H*,3*H*)-imidazol-2-one (5). To a solution of **3a** (2.25 g, 10 mmol) in pyridine (12 ml) 4-nitrobenzenesulfonyl chloride (2.3 g, 10 mmol) was added as a solid in several portions with stirring. After an exothermic reaction had completed, the reaction mixture was stirred at room temperature for 3 h. The resulting suspension was quenched with crushed ice (18 g) with stirring. The precipitate thus obtained was collected by filtration, washed successively with water and methanol, then dried to give **5** as a white amorphous powder (3.3 g, 81%, m.p. 252–254°C dec.). IR (KBr) cm^{-1}: 1740, 1530, 1380, 1340, 1180, 1140. ^{1}H NMR (DMSO-d_6) δ: 7.28 (s, 2H, H-4 and H-5, imidazo.), 7.60–7.93 (m, 5H, aromatic), 8.15–8.20 (m, 2H, aromatic), 8.39–8.45 (m, 2H, aromatic). ^{13}C NMR (DMSO-d_6) δ: 111.31, 112.01, 124.99, 127.79, 129.64, 129.83, 135.47, 140.34, 145.75, 150.21. Anal. Calcd. for $C_{15}H_{11}N_3O_7S_2$: C, 44.0; H, 2.7; N, 10.3. Found: C, 44.1; H, 2.8; N, 10.3.

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