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Synthesis and Antimicrobial Testing of Some Flavonylsulfonamide Derivatives

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Six new 4-amino-N-heteroaryl,N-[(2-phenyl-4*H*-1-benzopyran-4-oxo-6-yl)metil]benzensulfonamide derivatives, (3a-3f) were prepared by reacting 6-bromomethylflavone with the corresponding sulfonamide derivatives and their antimicrobial activities against *Escherichia coli* were evaluated. All of the compounds exhibited better activity (except compound 3c) than the corresponding sulfonamide derivatives.

Key Words: Flavonylsulfonamides, synthesis, antimicrobial

Introduction

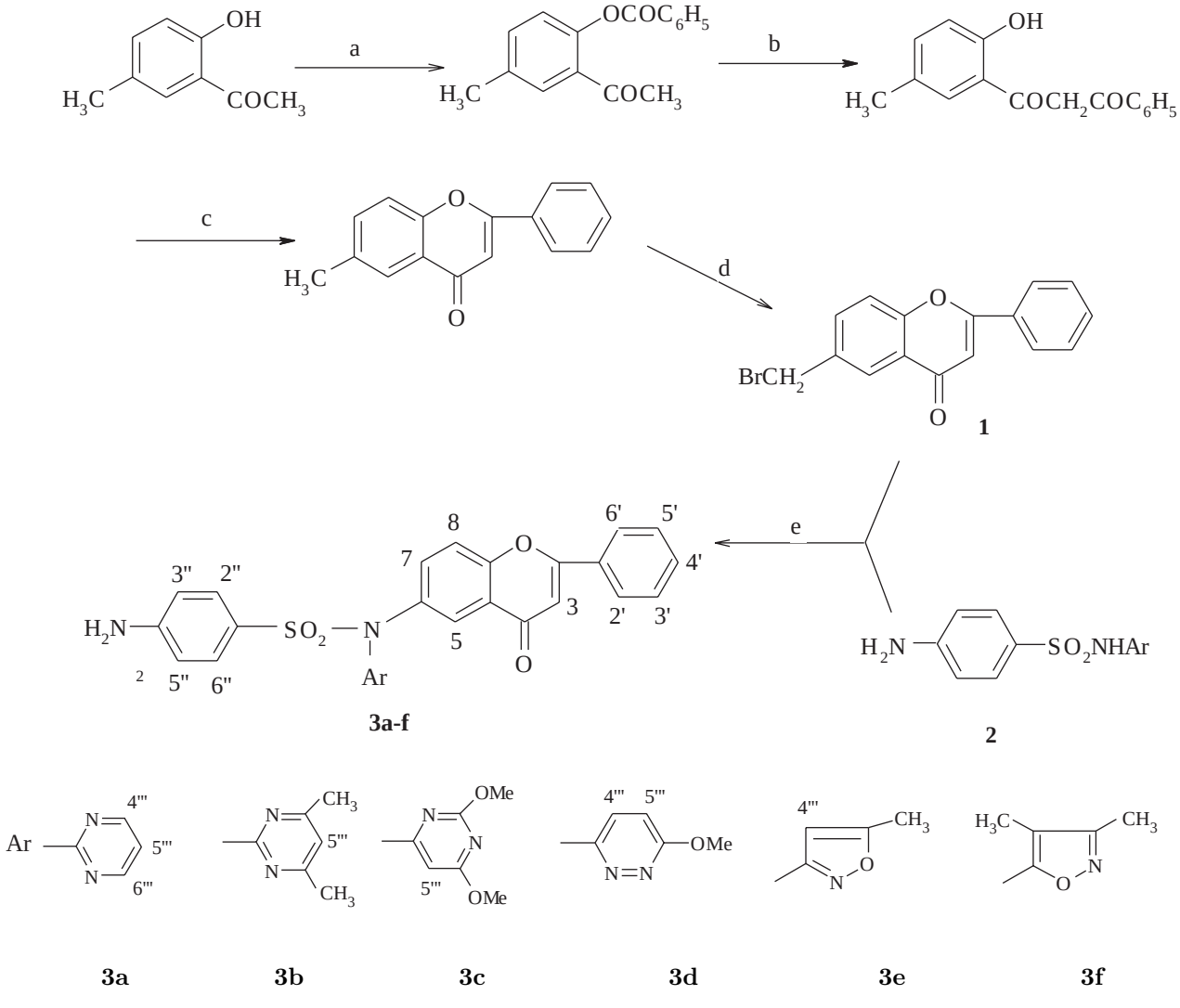
The flavone ring system is present in many naturally occurring products[1], and the flavone derivatives display a wide spectrum of biological activities such as antibacterial[2], antifungal[3], antiviral[4], antitumor[5], antioxidant[6], spasmolytic[7], hypoglycemic[8,9] and antihistaminic[10]. Furthermore, it is well documented that sulfonamide derivatives have been used in antimicrobial chemotherapy[11]. In view of previous reports indicating that derivatives of flavone exhibit antimicrobial activity[12−14] we report the synthesis and antimicrobial evaluation of new sulfonamide derivatives with a flavone ring system.

Experimental

Melting points were determined with Büchi SMP-20 melting point apparatus and are uncorrected. IR spectra were recorded on a Jasco FT/IR 420 spectrometer by KBr discs. ^{1}H NMR spectra were measured with a Bruker GmbH DPX-400, 400 MHz instrument using TMS as the internal standard and DMSO-d_6 as the solvent. All chemical shifts were reported as δ (ppm) values. EIMS were obtained with a VG Platform II, Micromass spectrometer with ionization energy maintained at 70 eV. Elemental analysis (C,H,N) was performed on a Leco CHNS 932 instrument and the results were within $\pm 0.4\%$ of the theoretical values. All instrumental analysis was performed at the Scientific and Technical Research Council of Turkey, Instrumental Analysis Center (Ankara, Turkey).

The chemical reagents used in the synthesis were purchased from E. Merck, Aldrich and Sigma. Column chromatography was carried out on silica gel 60 (230-400 mesh ASTM). The ATCC strains of the microorganism used in this study were obtained from the culture collection of the Refik Saydam Health Institution of the Health Ministry, Ankara-Turkey.

6-Bromomethylflavone was synthesized starting from 2'-hydroxy-5'methylacetophenone in line with to the literature[15] (Figure).



a: Benzoylchloride/pyridine, b: KOH/pyridine, c: Conc.H_2SO_4, d: N-Bromosuccinimide/benzoylperoxide, e: Anhydrous K_2CO_3/DMF

Figure. Synthesis of the compounds.

General Synthesis of Compounds 3a-3f

A mixture of (157 mg, 0.5 mmol) 6-bromomethylflavone **(1),** 0.5 mmol of appropriate sulfonamides **(2)** and anhydrous potassium carbonate (69 mg, 0.5 mmol) was stirred at 60 °C in 10 mL DMF until the starting

materials were used up. Water was added and the mixture was extracted with $CHCl_3$. The extract was washed with water and purified by column chromatography. Some physico-chemical properties, spectral data and purification solvents of the prepared compounds are given in Tables 1 and 2.

Table 1. Physical and spectral data of compounds 3a-3f.

No	Yield	M.p (^{o}C)	^{1}H NMR (δ ppm)	Mass m/z (%)
3a	17	260	5.49 (s, 2H, CH_2), 6.18 (s, 2H, NH_2), 6.59 (d, 2H, J_o = 8.69 Hz, H-3",5"), 7.09 (s, 1H, H-3), 7.13 (td, 1H, J_o = 4.85 Hz, H-5"'), 7.63-7.66 (m, 3H, H-3',4',5'), 7.69 (d, 2H, J_o = 8.67 Hz, H-2",6"), 7.83-7.85 (m, 2H, H-7,8), 8.09 (s, 1H, H-5), 8.15 (d, 2H, J_o = 7.11 Hz, H-2',6'), 8.61 (d, 2H, J_o = 4.83 Hz, H-4"',6"')	333 (1.71), 249 (2.40), 222 (84.85), 102 (54.04), 92 (77.78), 65 (50.76), 44 (100)
3b	47	230	2.32 (s, 6H, 4,6-CH_3), 5.48 (s, 2H, CH_2), 6.14 (s, 2H, NH_2), 6.58 (d, 2H, J_o = 7.03 Hz, H-3",5"), 6.87 (s, 1H, H-5"'), 7.09 (s, 1H, H-3), 7.63-7.67 (m, 3H, H-3',4',5'), 7.68 (d, 2H, J_o = 7.05 Hz, H-2",6"), 7.81 (d, 1H, J_o = 8.64 Hz, H-8), 7.88 (dd, 1H, J_o = 8.68 Hz, J_m = 2.22 Hz, H-7), 8.14-8.16 (m, 3H, H-5, 2', 6')	356 (2.88), 250 (21.16), 235 (7.92), 92 (27.72), 65 (33.66), 44 (100)
3c	66	179	3.77 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.42 (s, 2H, CH_2), 6.32 (s, 2H, NH_2), 6.48 (s, 1H, H-5"'), 6.65 (d, 2H, J_o = 8.73 Hz, H-3",5"), 7.08 (s, 1H, H-3), 7.57-7.65 (m, 5H, H-3',4',5',2",6"), 7.81-7.85 (m, 2H, H-7,8), 8.09-8.14 (m, 3H, H-5,2',6')	544 ($M^{+\cdot}$) (1.72), 222 (10.11), 133 (19.31), 92 (70.79), 65 (100), 44 (40.59)
3d	49	262	3.87 (s, 3H, OCH_3), 5.49 (s, 2H, CH_2), 5.81 (s, 2H, NH_2), 6.52 (d, 2H, J_o = 8.67 Hz, H-3", 5"), 7.12 (s, 1H, H-3), 7.43 (d, 2H, J_o = 8.66 Hz, H-2",6"), 7.46 (d, 1H, J = 9.95 Hz, H-5"'), 7.62-7.67 (m, 3H, H-3',4',5'), 7.80-7.84 (m, 2H, H-7,8), 7.99 (d, 1H, J = 9.94 Hz, H-4"'), 8.10 (d, 1H, J_m = 1.52 Hz, H-5), 8.16 (dd, 2H, J_o = 8.14 Hz, J_m = 1.88 Hz, H-2',6')	358 (8.37), 222 (1.96), 156 (7.54), 133 (19.09), 102 (42.36), 65 (20.94), 44 (100)
3e	16	235	2.35 (s, 3H, CH_3), 5.02 (s, 2H, CH_2), 6.24 (s, 2H, NH_2), 6.51 (s, 1H, H-4"'), 6.65 (d, 2H, J_o = 8.82 Hz, H-3",5"), 7.09 (s, 1H, H-3), 7.53 (d, 2H, J_o = 8.81 Hz, H-2",6"), 7.52-7.55 (m, 3H, H-3',4',5'), 7.80-7.82 (m, 2H, H-7,8), 8.06 (s, 1H, H-5), 8.15 (d, 2H, J_o = 6.12 Hz, H-2',6')	333 (1.51), 222 (3.68), 102 (35.71), 92 (4.13), 77 (8.59), 55 (100)
3f	32	239	1.49 (s, 3H, CH_3), 1.92 (s, 3H, CH_3), 4.58 (s, 2H, CH_2), 6.09 (s, 2H, NH_2), 6.53 (d, 2H, J_o = 8.81 Hz, H-3",5"), 6.88 (s, 1H, H-3), 7.29 (d, 2H, J_o = 8.79 Hz, H-2',6'), 7.40-7.48 (m, 3H, H-3',4',5'), 7.56 (dd, 1H, J_o = 8.68 Hz, J_m = 2.16 Hz, H-7), 7.59 (d, 1H, J_o = 8.63 Hz, H-8), 7.79 (d, 1H, J_m = 1.96 Hz, H-5), 7.94 (dd, 2H, J_o = 8.18 Hz, J_m = 1.88 Hz, H-2",6")	501 ($M^{+\cdot}$) (0.3), 235 (10.79), 222 (3.52), 156 (6.51), 102 (6.84), 83 (100), 65 (10.59), 44 (12.37)

Antimicrobial Activity

A paper disc (8 mm in diameter) was soaked in a 1500 μg/mL solution of the test compound in DMF and placed on an agar plate containing bacteria cells, which was incubated at 37 °C for 24 h. The diameter of

the growth inhibition zone around the paper disc was measured[16]. The antimicrobial acitivity results of the compounds are shown in Table 2.

Table 2. Antimicrobial activities and purification solvents of the compounds.

No.	Formula	Purification solvent	Antimicrobial Activity	
				Escherichia coli
			Sulfadiazine	8
3a	$C_{26}H_{20}N_4O_4S$	$CHCl_3$-Acetone-NH_3 (10:1:0.1)		11
			Sulfamethazine	6
3b	$C_{28}H_{24}N_4O_6S$	$CHCl_3$-Isopropanol (10:1)		7
			Sulfadimethoxine	9
3c	$C_{26}H_{21}N_3O_5S$	$CHCl_3$-Isopropanol (10:2)		6
			Sulfamethoxypyridazine	5
3d	$C_{27}H_{23}N_3O_5S$	$CHCl_3$-Isopropanol-NH_3 (10:1:0.1)		8
			Sulfamethoxazole	8
3e	$C_{27}H_{22}N_4O_4S$	$CHCl_3$-Acetone (10:2)		9
			Sulfisoxazole	5
3f	$C_{27}H_{22}N_4O_5S$	$CHCl_3$-Acetone (10:1)		7

Results and Discussion

6- Bromomethylflavone (1) was synthesized according to the literature method [15]. Flavonylsulfonamide derivatives were prepared by reacting 6-bromomethylflavone (1) with the selected sulfonamide derivatives (2) in DMF/anhydrous K_2CO_3 with yield of 17-66% as outlined in the Figure. All spectral data were in accordance with the assumed structures. In ^{1}H NMR spectra, all aromatic/heteroaromatic protons were between 6.48 and 8.61 ppm, and -CH_2- and aromatic NH_2 protons were 4.58-5.49 and 5.81-6.32 ppm as a singlet, respectively. Mass spectrometric analyses were performed by the electron impact (EI) method. Compounds 3c and 3f showed molecular ion peaks. The ion peaks m/z = 44; m/z = 55; m/z = 65 and m/z = 83 are the base peaks for compounds 3a, 3b and 3d, 3e, 3c and 3f, respectively. Other fragments appeared at the expected m/z values. All new compounds were tested for their antimicrobial activity against *E. coli* by

the agar diffusion method and the results were compared to the corresponding sulfonamide derivatives. As seen in Table 2, all of the compounds except 3c showed better activity against *E. coli* than the corresponding sulfonamides.

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