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Short Note

2-Methoxy-5-{4-oxo-2-[(*E*)-2-(4-sulfamoylphenyl)ethenyl-3,4-dihydroquinazolin-3-yl]benzene-1-sulfonamide

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Abstract: The title compound, 2-methoxy-5-{4-oxo-2-[(*E*)-2-(4-sulfamoylphenyl) ethenyl-3, 4-dihydroquinazolin-3-yl] benzene-1-sulfonamide **2** has been synthesized by the reaction of 3-(4-methoxyphenyl)-2-styryl-4(3*H*)-quinazolinone **1** with an excess of chlorosulfonic acid, followed by amidation of the sulfonyl chloride product with ammonia gas. The structure of the synthesized compound was confirmed on the basis of IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data.

Keywords: 4(3*H*)-quinazolinone; 2-styryl-4(3*H*)-quinazolinone; benzenesulfonamide; chlorosulfonation-amidation

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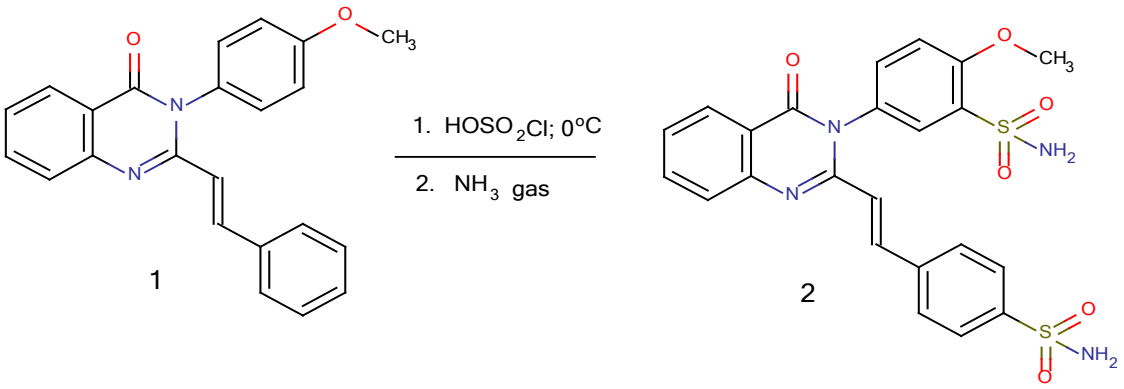
Compounds containing the 4(3*H*)-quinazolinone ring system possess various biological activities [1]. Some 4(3*H*)-quinazolinone derivatives have been synthesized and evaluated as potent and tolerable anti-inflammatory agents and are reported to exhibit significant COX-2 inhibition and anti-inflammatory activity [2,3]. The majority of COX-2 inhibitors are diarylheterocycles. The presence of para-sulfonamide or para-sulfonylmethane substituents at one of the phenyl rings was found to be essential for optimum COX-2 selectivity and inhibitory potency. A wide variety of heterocycles (five-membered or six-membered rings) can serve as central ring system of the diarylheterocyclic structures [4,5]. The results of a molecular docking study showed that a 2,3-disubsituted-4(3*H*)-quinazolinone possessing a *p*-benzenesulfonamide moiety at C-2 and a phenyl ring at N-3 was

predicted to have potent COX-2 inhibitory activity [6]. The one-pot reaction sequence of chlorosulfonation-amidation was reported for the synthesis of sulfonamide-substituted diarylheterocycles, a class of selective COX-2 inhibitors [5,7]. In this paper, we report chlorosulfonation-amidation of 3-(4-methoxyphenyl)-2-styryl-4(3*H*)-quinazolinone **1**.

The starting material **1** was prepared according to a reported method [1,8–10]. Compound **1** was reacted with an excess of chlorosulfonic acid at 0 °C to give a sulfonyl chloride product, then followed by treatment of the sulfonyl chloride with ammonia gas to produce 2-methoxy-5-{4-oxo-2-[(*E*)-2-(4-sulfamoylphenyl)ethenyl-3,4-dihydroquinazolin-3-yl]benzene-1-sulfonamide **2** (Scheme 1).

Scheme 1.



The IR spectrum of compound **2** showed absorption bands at 3373 and 3273 cm^{-1} due to the presence of NH_2. The bands at 1335 and 1157 cm^{-1} correspond to -SO_2-. In the ^{1}H-NMR spectrum, four protons of two sulfonamide NH_2 groups appear as two broad singlets at δ 7.29 and 7.40 ppm, while the four protons of the quinazolinone ring are observed as two triplets at δ 7.56 ppm (1H, *J* = 7.8 Hz, H-6) and δ 7.89 ppm (1H, *J* = 7.8 Hz, H-7), and two double doublets at δ 7.69 ppm (1H, *J* = 7.8, 2.6 Hz, H-8) and δ 8.l4 ppm (1H, *J* = 7.8, 1.3 Hz, H-5). Protons of the two phenyl rings appear at: δ 7.41 ppm (1H, d, *J* = 9.0 Hz, H-3'), δ 7.62 ppm (2H, d, *J* = 8.5 Hz, H-2"/6"), δ 7.78 ppm (3H, d, *J* = 8.3 Hz) and δ 7.82 ppm (1H, *J* = 2.15 Hz). The appearance of a proton of the phenyl ring as doublet at δ 7.82 ppm (1H, *J* = 2.15 Hz) indicates that the –SO_2NH_2 group subtituted an H of the phenyl ring at *ortho* position from the proton and methoxy group. The three protons of the phenyl ring observed as doublet at δ 7.78 ppm (*J* = 8.3 Hz) were described as overlapping of H-4' and H-3"/5". The appearance of the four protons as two doublets at δ 7.62 ppm (2H, *J* = 8.5 Hz, H-2"/6") and δ 7.78 ppm (2H, *J* = 8.3 Hz, H-3"/5") in the ^{1}H-NMR spectrum and two pairs of symmetrical carbon atoms at δ 128.1 and δ 126.4 ppm in the ^{13}C-NMR spectrum indicated that the second –SO_2NH_2 group subtituted a H at *para* position of the phenyl ring attached to the ethenyl chain. The structure is further supported by the HRESIMS of compound **2** which shows the molecular ion peak at *m/z* 513.0894 ($[M+H]^+$). This value is in complete agreement with the structure assigned.

Experimental

Chlorosulfonic acid (2 mL, 16 mmol) was added dropwise to **1** (1.0 g, 3.2 mmol) at 0 °C with vigorous stirring under anhydrous conditions. The cooling bath was removed and the reaction was allowed to proceed for 6 h at 25 °C. The cooled reaction mixture was poured slowly onto crushed ice

and the benzenesulfonyl chloride intermediate product was isolated by rapid filtration to reduce the exposure time to moisture. This product was dissolved in tetrahydrofuran (THF) (60 mL), and then gaseous ammonia was bubbled through the solution for 10 min at 25 °C. The solvent was removed *in vacuo* to give a residue, that was suspended in hot water. The hot suspension was filtered and the solid was recrystallized from acetonitrile. The crystals obtained were washed with cold ethanol (95%) and dried in a vacuum oven at 80 °C for 24 h.

Yield: 17%, m.p. 284–285 °C, pale yellow crystalline powder.

IR (KBr), υ_{max} cm^{-1}: 3381, 3235 (primary sulfonamide N-H streching), 3069 (aromatic/alkene C-H streching), 2945 (alkyl C-H streching), 1663 (C = O lactam), 1607 (C = N), 1550 (C = C), 1270 (aryl alkyl ether, Ar-O-C), 1338 and 1161 (sulfonamide asymetric and symetric SO_2 streching) [11].

^{1}H-NMR (500 MHz, DMSO-d_6, TMS), δ/ppm: 8.14 (1H, dd, J = 7.8, 1.3 Hz, 5-$H_{quinazolinone}$), 7.93 (1H, d, J = 15.6 Hz, 2-$H_{trans\text{-}ethenyl}$), 7.89 (1H, t, J = 7.8 Hz, 7-$H_{quinazolinone}$), 7.82 (1H, d, J = 2.15 Hz, 6'-$H_{Phe\text{-}X}$), 7.78 (3H, d, J = 8.3 Hz, overlapping of 3",5"-$H_{Phe\text{-}Y}$ and 4'-$H_{Phe\text{-}X}$), 7.69 (1H, dd, J = 7.8, 2.6 Hz, 8-$H_{quinazolinone}$), 7.62 (2H, d, J = 8.2 Hz, 2",6"-$H_{Phe\text{-}Y}$), 7.56 (1H, t, J = 7.8 Hz, 6-$H_{quinazolinone}$), 7.41 (1H, d, J = 9 Hz, 3'-$H_{Phe\text{-}X}$), 7.4 (2H, s, broad, $NH_{2sulfonamide}$), 7.29 (2H, s, broad, $NH_{2sulfonamide}$), 6.5 (1H, d, J = 15.6 Hz, 1-$H_{trans\text{-}ethenyl}$), 4.01 (3H, s, OCH_3) [11]. Phe-X = 2'-OMe-benzene-1'-sulfonamide. Phe-Y = 4"-sulfamoyl-phenylethenyl.

^{13}C-NMR (125 MHz, DMSO-d_6, TMS), δ/ppm: 161.5 (C(= O)-N, C-$4_{quinazolinone}$), 156.3 (-N-C = N-, C-$2_{quinazolinone}$), 151.2 ($C_{Phe\text{-}O}$), 147.3 ($C_{Phe\text{-}N=C}$, C-$9_{quinazolinone}$), 144.6 (C-4"$_{Phe\text{-}4"\text{-}sulfonamide}$), 128.1 (C-2",6"$_{Phe\text{-}4"\text{-}sulfonamide}$), 126.4 (C-3",5"$_{Phe\text{-}4"\text{-}sulfonamide}$), 56.6, ($OCH_3$) 138.0 , 137.4, 134.3, 131.9,113.7, 134.9, 128.4, 128.3, 127.4, 126.9, 126.5, 122.5, and 120.8 (C aromatic and C ethenyl) [11].

HRESIMS (*m/z*): found 513.0894 ($[M+H]^+$), calculated masses of $C_{23}H_{20}N_4O_6S_2$: 513.0903 (error 1.8 ppm) (ACS acceptable limits error for HRMS is 5 ppm). The mass spectrum was measured with a Waters LCT Premier XE (ESI-TOF) on positive mode.

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