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ORIGINAL ARTICLE

Synthesis and biological evaluation of new sydnone based derivatives

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Abstract An extensive characterization study on the novel series of synthesized sydnone, chalcone and pyrimidine is reported in this paper. A series of 3-(4-chlorophenyl)-4-{[4-(3-substitutedphenylacryloyl)phenyl]sulfamoyl}-sydnone and 3-(4-chlorophenyl)-4-[4-(4-aminophenyl)-6-substitutedphenylpyrimidin-2-aminesulfonyl]-sydnone are synthesized. The structures of the synthesized compounds were characterized by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. An exclusive study on microbial activity using various microbial strains was also undertaken to support and confirm our experimental findings.

1. Introduction

Sydnones are most important member of the mesoionic category of compounds. Sydnone derivatives have been viewed as exotic structures within the heterocyclic community. With few exceptions, sydnones are stable compounds that exhibit significant polarity. A hydrogen atom at the fourth position of the sydnone ring allows substitution with a wide variety of electrophiles, with retention of the ring, typical of aromatic substrates (Asundaria and Patel, 2010). A large number of sydnone derivatives have been synthesized (Ollis and Ramsden, 1976; Kier and Roche, 1967) as they serve to be vital biological agents viz, antitumor (Bos and Leischhacker, 1984) antiviral (Dunkley and Thoman, 2003), analgesic, anti-inflammatory, anthelmintic (Mukesh and Tandon, 2006), antimicrobial (Kalluraya et al., 2002), free radical scavenging (Kavali and Badami, 2000) and nitric oxide donor (Mallur et al., 2007), activities. Present study seeks to synthesized series of novel chalcone (Al-Jaber et al., 2012), and Pyrimidine (Patel and Mehta, 2010; Hussein, 2010), derivatives that contain such important sydnonyl moiety, with the aim of obtaining new biologically active compounds. As a part of this work we have used sydnone based α-β-unsaturated ketone derivatives (chalcone) as useful precursors in the synthesis of the corresponding pyrimidine derivatives. Sydnones exhibit biological activities (Reddy and Sarma Rama, 1993; Prasad et al., 2008; Lim et al., 2007; Mishra et al., 2008; Rani et al., 2004), similar to pyrimidine which is the basic nucleus in DNA and RNA. Studies have claimed the use of pyrimidine derivatives efficient curing drug for thyroid and leukemia (Supaluk et al., 2009). In view of the continued interest in developing the simpler and

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more convenient synthetic routes several sydnone based heterocyclic systems were investigated (Jin et al., 2007; Cheng et al., 2008).

2. Results and discussion

2.1. Chemistry

The synthesis of sydnone, chalcone and pyrimidine derivatives examined are shown in the Scheme 1. Initial step involves the dehydration of *N*-alkyl or aryl *N*-nitroso-α-amino acid which is the only general route to sydnones. For the formation of sydnones by ring closure of N-substituted *N*-nitrosoglycines, it is evident that at least one hydrogen atom is required on the α-carbon atom and that the amino nitrogen atom should have a substituent other than hydrogen. However, when an *N*-alkyl-*N*-nitroso-α-amino dicarboxylic acid is treated with acetic anhydride, sydnone ring competes with the cyclic acid anhydride formation by dehydration between the two carboxyl groups and the result is rather complicated. In the case of nitrosoiminodiacetic acid, 3-carboxy methyl sydnone is obtained instead of the corresponding cyclic anhydride (Stewart, 1963). Synthesis of 3-(4-chlorophenyl)-4-[4(acetylphenyl)sulfamoyl]-sydnone as described in the scheme. Chalcones (**8a–j**) were carried out by condensing 3-(4-chlorophenyl)-4-[4(acetylphenyl) sulfamoyl]-sydnone with different substituted aldehyde in dilute ethanolic sodium hydroxide solution at room temperature. The compounds (**9a–j**) were synthesized by the reaction of the chalcones (**8a–j**) with guanidine nitrate using sodium ethoxide in ethanol. Yield of the novel compounds were found between 62% and 89% depending upon reactivity of the substituted aldehyde.

All the compounds gave satisfactory elemental analysis. IR and NMR spectral measurements confirmed the correct approach of synthesis. The expected spectral features of synthesized compounds have been assigned.

Compounds belonging to **8a–j** series showed typical sharp absorptions at υ_{max} 1773 cm^{-1} which is characteristic –C═O band of the sydnone, a sharp band of styryl –C═O at 1662 cm^{-1}, –CH═CH– of chalcone at 1599 cm^{-1} and the asymmetric and symmetric band of $–SO_2$ at 1353 cm^{-1} and 1173 cm^{-1}, respectively, were observed. The ^{1}H NMR spectra exhibited doublet at δ 6.65–6.67 ppm which attributed the ═CH–CO– protons and second doublet at δ 7.38–7.41 ppm confirmed the presence of $═CH_2$-Ar group. In ^{13}C NMR of the chalcone, the –CH═CH– carbon signals appeared at the δ 146.47 and 123.48 ppm, respectively. The high-field resonance at δ 190.76 ppm was attributed to the carbonyl group present in chalcone. The structures of compounds **9a–j** were also confirmed using IR and NMR spectroscopy. The IR spectra of the pyrimidine showed no styryl –C═O band at 1662 cm^{-1} but there were new asymmetric and symmetric broad bands at 3355 and 3220 cm^{-1}, respectively, for $–NH_2$. Signals at δ 5.15 ppm and δ 7.85 ppm for the $–NH_2$ and –CH of the pyrimidine ring were observed in ^{1}H NMR spectrum and the pyrimidine –CH carbon resonance appeared at δ 102.38 ppm in the ^{13}C NMR spectra. On the basis of the above spectral data the structures of the compounds **8a–j** and **9a–j** compounds were confirmed.

2.2. Experimental

2.2.1. General

All the melting points reported are uncorrected and were recorded using an Electro Thermal Melting Point apparatus. Elemental analyses (C, H and N) were performed at G.N.F.C. (Gujarat Narmda Valley Fertilizer Company Ltd., Bharuch). Fourier transform infrared spectra were recorded with a Thermo Scientific Nicolet ISO-10 spectrophotometer in the frequency range 4000–400 cm^{-1} with samples embedded in KBr discs. Proton nuclear magnetic resonance (^{1}H NMR) spectra of the compound were recorded with a Bruker Avance II 400 NMR using DMSO-d_6 as a solvent and tetramethylsilane as an internal reference. Carbon (^{13}C) NMR spectra of the compounds were recorded with a Bruker Avance II 400 NMR spectrometer at SAIF (Sophisticated Analytical Instrument Facilities), Chandigarh. Thin-layer chromatography analyses were performed by using aluminium-backed silica-gel plates (Merck 60 F524) and examined under short-wave ultraviolet (UV) light.

2.2.2. Synthesis of ethyl N-(4-chlorophenyl)glycinate (2)

p-Chloroaniline (1.40 g, 1.0 mmol), chloroethyl acetate (1.06 mL, 0.01 mol) in ethanol (10 mL) and anhydrous sodium acetate (1.64 g, 2.0 mmol) were refluxed for 5 h. The mixture was diluted with 10 mL of water and kept in refrigerator overnight. Recrystallization in ethanol gave 81% yield of pure glycinate. M.p. 116 °C. IR (KBr): 3328 cm^{-1}(N–H Str.), 2951, 2887 cm^{-1}, (C–H Str. aliphatic), 1757 (C–O Str. of ester), 1604, 1511 cm^{-1} (C═C Str. of aromatic), 1072, 750 cm^{-1} (C–Cl), ^{1}H NMR (DMSO-d_6): δ 1.21 (t, 3H, $COOCH_2CH_3$), 3.76 (s, 1H, NH), 4.29 (s, 2H, CH_2), 4.54 (q, 2H, $COOCH_2CH_3$), 6.83–7.21 (m, 4H, Ar- H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 14.67 ppm (CH_3), 115.12–146.26 ppm (Ar-C), 172.11 ppm (C–O).

2.2.3. Synthesis of N-(4-chlorophenyl)glycine (3)

Compound **2** (2.13 g, 1.0 mmol) and sodium hydroxide (0.6 g, 1.5 mmol) in solution of distilled water and ethanol (18:4 mL) was heated at 80–85 °C for 0.5 h. Allowed to cool and acidified with hydrochloric acid. Crystalline white product was obtained. Yield 78%. M.p. 146 °C. IR (KBr): 3323 cm^{-1}(N–H Str.), 3278 cm^{-1} (O–H Str. of acid), 1705 cm^{-1} (C–O Str. of acid), 1604, 1511 cm^{-1} (C═C Str. of aromatic), 1067, 750 cm^{-1} (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.33 (s, 2H, CH_2), 6.44 (s, 1H, COOH), 6.52 (s, 1H, NH), 6.88–7.23 (m, 4H, Ar-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 114.32–146.07 ppm (Ar-C), 172.18 ppm (C–O).

2.2.4. Synthesis of [(4-chlorophenyl)(nitroso)amino]acetic acid (4)

To an ice cooled solution of the **3** (1.86 g, 1.0 mmol) in water (40 mL), a solution of sodium nitrite (0.69 g, 1.0 mmol) in water (5 mL) was added drop wise with stirring. The reaction mixture was filtered and precipitated by adding concentrated hydrochloric acid to the filtrate. Yellowish needles were obtained as product. Yield 84%. M.p. 105 °C. IR (KBr): 3257 cm^{-1} (O–H Str. of acid), 1712 cm^{-1} (C–O Str. of acid), 1604, 1511 cm^{-1} (C═C Str. of aromatic), 1571, 1328 cm^{-1} (N═O), 1065, 750 cm^{-1} (C–Cl); ^{1}H NMR(400 MHz, DMSO-d_6): δ 5.02 (s, 2H, CH_2), 6.93–7.48 (m, 4H, Ar-H),