PUBLICATION
Synthesis and biological evaluation of new sydnone based derivatives

Yogesh M. Patel, Keshav C. Patel *

Department of Chemistry, Veer Narmad South Gujarat University, Surat 395 007, Gujarat, India

Received 11 January 2012; accepted 29 February 2012

KEYWORDS
Sydnone; Chalcone; Pyrimidine; Microbial studies

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-substitutedphenylacetyl)phenyl]sulfamoyl}-sydnone and 3-(4-chlorophenyl)-4-[4-(4-aminophenyl)-6-substitutedphenylpyrimidin-2-aminosulfonyl]-sydnone are synthesized. The structures of the synthesized compounds were characterized by elemental analysis, IR, 1H NMR, 13C 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 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 sydones. For the formation of sydrones 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 $\lambda_{\text{max}}$ 1773 cm$^{-1}$ which is characteristic –C=O of the sydnone, a sharp band of styril 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$^{-1}$, respectively, were observed. The 1H NMR spectra exhibited doublet at $\delta$ 6.65–6.67 ppm which attributed the –CH$_2$– protons and second doublet at $\delta$ 7.38–7.41 ppm confirmed the presence of –CH$_2$-Ar group. In 13C NMR of the chalcone, the –CH=CH– carbon signals appeared at the $\delta$ 146.47 and 123.48 ppm, respectively. The high-field resonance at $\delta$ 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 styril –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 $\delta$ 5.15 ppm and $\delta$ 7.85 ppm for the –NH$_2$ and –CH of the pyrimidine ring were observed in 1H NMR spectrum and the pyrimidine –CH carbon resonance appeared at $\delta$ 102.38 ppm in the 13C 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 Narmada Valley Fertilizer Company Ltd., Bharuch). Fourier transform infrared spectra were recorded with a Thermoscientific Nicolet ISO-10 spectrophotometer in the frequency range 4000–400 cm$^{-1}$ with samples embedded in KBr discs. Proton nuclear magnetic resonance (1H 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 (13C) 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 (Merek 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$^{-1}$ (O–H Str. of acid), 1712 cm$^{-1}$ (C–O Str. of aromatic), 1072, 750 cm$^{-1}$ (C–Cl). 1H NMR (DMSO-d$_6$): $\delta$ 1.21 (t, 3H, COOCH$_2$CH$_3$), 3.76 (s, 1H, NH), 4.29 (s, 2H, CH$_2$), 4.54 (q, 2H, COOCH$_2$CH$_3$), 6.83–7.21 (m, 4H, Ar, H); 13C NMR (400 MHz, DMSO-d$_6$): $\delta$ 14.67 ppm (CH$_3$), 115.12–146.26 ppm (Ar-C), 172.11 ppm (C=O) (Ar-C).

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$^{-1}$ (C–OH Str.), 3278 cm$^{-1}$ (O–H Str. of acid), 1705 cm$^{-1}$ (C=O Str. of acid), 1604, 1511 cm$^{-1}$ (C=O Str. of aromatic). IR (KBr): 3323 cm$^{-1}$ (C–OH Str.), 3278 cm$^{-1}$ (O–H Str. of acid), 1705 cm$^{-1}$ (C=O Str. of acid), 1604, 1511 cm$^{-1}$ (C=O Str. of aromatic). IR (KBr): 3323 cm$^{-1}$ (C–OH Str.), 3278 cm$^{-1}$ (O–H Str. of acid), 1705 cm$^{-1}$ (C=O Str. of acid), 1604, 1511 cm$^{-1}$ (C=O Str. of aromatic).

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 with diethyl ether to obtain product. Yield 84%. M.p. 100 °C. IR (KBr): 3257 cm$^{-1}$ (O–H Str. of acid), 1712 cm$^{-1}$ (C–O Str. of acid), 1604, 1511 cm$^{-1}$ (C=O Str. of aromatic). IR (KBr): 3257 cm$^{-1}$ (O–H Str. of acid), 1712 cm$^{-1}$ (C–O Str. of acid), 1604, 1511 cm$^{-1}$ (C=O Str. of aromatic). IR (KBr): 3257 cm$^{-1}$ (O–H Str. of acid), 1712 cm$^{-1}$ (C–O Str. of acid), 1604, 1511 cm$^{-1}$ (C=O Str. of aromatic). IR (KBr): 3257 cm$^{-1}$ (O–H Str. of acid), 1712 cm$^{-1}$ (C–O Str. of acid), 1604, 1511 cm$^{-1}$ (C=O Str. of aromatic). IR (KBr): 3257 cm$^{-1}$ (O–H Str. of acid), 1712 cm$^{-1}$ (C–O Str. of acid), 1604, 1511 cm$^{-1}$ (C=O Str. of aromatic). IR (KBr): 3257 cm$^{-1}$ (O–H Str. of acid), 1712 cm$^{-1}$ (C–O Str. of acid), 1604, 1511 cm$^{-1}$ (C=O Str. of aromatic).

11.56 (s, 1H, COOH); $^{13}$C NMR (400 MHz, DMSO-$d_6$): $\delta$ 120.78–138.89 ppm (Ar-C), 168.24 ppm (C–O).

2.2.5. Synthesis of 3-(4-chlorophenyl)sydnone (5)

The mixture of 4 (2.70 g, 1.26 mmol) and acetic anhydride (15 mL) was stirred at room temperature for 12 h in dark. The solution was poured slowly into cold water which was very well stirred. The pH of the content was adjusted to 7.0 with 10% sodium bicarbonate solution. The crude sydnone obtained was washed well with water and dried. Recrystallization from 95% ethanol afforded yield 98% of light yellow needles, m.p. 140–145 °C. IR (KBr): 3078 cm$^{-1}$ (C–H of aromatic), 1156 (C=O, OD) cm$^{-1}$.

Scheme 1 3-(4-Chlorophenyl)-4-[4-(3-substituted phenyl acryloyl) phenyl] sulfamoyl]-sydnone (8a–j) and 3-(4-chlorophenyl)-4-(N-(4-(2-amino-4-(substitutedphenyl) pyrimidin-5-yl) phenyl) sulfamoyl)-sydnone (9a–j).

R= a; 4-OCH$_3$, b: 4-CH$_3$, c: 2-Cl, d: 2-NO$_2$, e: 4-F, f: 4-N(CH$_3$)$_2$, g: 4-Cl, h: 4-
OH, i: 2-OH-4-N(C$_2$H$_5$)$_2$, j: H
To a well stirred solution of the completion of reaction, it was poured into ice water, proaldehyde (1.0 mmol) in ethanol (98 mL) and 20% NaOH solution. Yield 89%. M.p. 168–171 °C. IR (KBr): 1777 cm\(^{-1}\) (C=O of sydnone), 1689 cm\(^{-1}\) (C=O of acetophenon), 1599 cm\(^{-1}\) (–CH=CH), 1345, 1347, 1174 cm\(^{-1}\) (Ar–C), 7.38 ppm (d, 1H, –CH), 7.59–8.07 ppm (m, 12H, Ar–H), 9.68 ppm (s, 1H, –SO2NH); \(^{13}\)C NMR (DMSO-d\(_6\)): δ 1056 ppm (CH of sydnone), 113.78–156.23 ppm (Ar–C), 123.77, 143.50 ppm (CH of sydnone), 115.13–160.17 ppm (Ar–C). 3-(4-Chlorophenyl)-4-(N-(4-(3-(2-nitrophenyl)acryloyl)phenyl)sulfamoyl)-sydnone (8d). Yield 70%. M.p. 137 °C. IR (KBr): 1751 cm\(^{-1}\) (–C=O, sydnone), 1660 cm\(^{-1}\) (–C=O, styryl ketone), 1595 cm\(^{-1}\) (–CH=CH), 1350, 1143 cm\(^{-1}\) (–SO2), 827 cm\(^{-1}\) (–C=O); \(^1\)H NMR (DMSO-d\(_6\)): δ 6.67 ppm (d, 1H, =CH–CO), 7.37 ppm (d, 1H, =CH), 7.60–8.07 ppm (m, 12H, Ar–H), 9.69 ppm (s, 1H, –SO2NH); \(^{13}\)C NMR (DMSO-d\(_6\)): δ 108.92 ppm (CH of sydnone), 117.13–160.12 ppm (Ar–C), 124.76, 144.10 ppm (CH=CH), 170.14 ppm (CH=O of sydnone), 190.27 ppm (O–CH of chalcone). MS: m/z (rel. int.%) 515 (M\(^+\)). Anal. (%) for C\(_{24}\)H\(_{18}\)N\(_3\)O\(_5\)SCl, Calcd: C, 58.12; H, 3.69; N, 8.46. 2.2.8.4. 3-(4-Chlorophenyl)-4-(N-(4-(3-(2-chlorophenyl)acryloyl)phenyl)sulfamoyl)-sydnone (8e). Yield 78%. M.p. 190 °C. IR (KBr): 1743 cm\(^{-1}\) (–C=O, sydnone), 1600 cm\(^{-1}\) (–C=O, styryl ketone), 1592 cm\(^{-1}\) (–CH=CH), 1349, 1166 cm\(^{-1}\) (–SO2), 814 cm\(^{-1}\) (–C=O); \(^1\)H NMR (DMSO-d\(_6\)): δ 6.65 ppm (d, 1H, =CH–CO), 7.37 ppm (d, 1H, =CH), 7.59–8.06 ppm (m, 12H, Ar–H), 9.68 ppm (s, 1H, –SO2NH); \(^{13}\)C NMR (DMSO-d\(_6\)): δ 109.32 ppm (CH of sydnone), 115.13–160.17 ppm (Ar–C), 123.21, 143.67 ppm (CH=CH), 171.56 ppm (C=O of chalcone), 192.16 ppm (C=O of chalcone); MS: m/z (rel. int.%) 515 (M\(^+\)). Anal. (%) for C\(_{25}\)H\(_{20}\)N\(_2\)O\(_5\)SCl, Calcd: C, 53.50; H, 2.93; N, 8.14; Found: C, 53.54; H, 2.97; N, 8.10. 2.2.8.5. 3-(4-Chlorophenyl)-4-(N-(4-(3-(4-(dimethylamino)phenyl)sulfamoyl)phenyl)sulfamoyl)-sydnone (8f). Yield 68%. M.p. 148 °C. IR (KBr): 1765 cm\(^{-1}\) (–C=O, sydnone), 1661 cm\(^{-1}\) (–C=O, styryl ketone), 1594 cm\(^{-1}\) (–CH=CH), 1355, 1150 cm\(^{-1}\) (–SO2), 976 cm\(^{-1}\) (–CF), 829 cm\(^{-1}\) (–C=O); \(^1\)H NMR (DMSO-d\(_6\)): δ 6.67 ppm (d, 1H, =CH–CO), 7.37 ppm (d, 1H, =CH), 7.59–8.08 ppm (m, 12H, Ar–H), 9.65 ppm (s, 1H, –SO2NH); \(^{13}\)C NMR (DMSO-d\(_6\)): δ 109.14 ppm (CH of sydnone), 115.13–160.12 ppm (Ar–C), 124.76, 144.10 ppm (CH=CH), 170.14 ppm (CH=O of sydnone), 190.27 ppm (O–CH of chalcone); MS: m/z (rel. int.%) 526 (M\(^+\)). Anal. (%) for C\(_{25}\)H\(_{22}\)N\(_2\)O\(_5\)SCl, Calcd: C, 52.43; H, 2.87; N, 10.63; Found: C, 52.49; H, 2.82; N, 10.67. 2.2.8.6. 3-(4-Chlorophenyl)-4-(N-(4-(3-(4-(dimethy lamino)phenyl)sulfamoyl)phenyl)sulfamoyl)-sydnone (8g). Yield 73%. M.p. 159 °C. IR (KBr): 3375 cm\(^{-1}\) (–OH), 1756 cm\(^{-1}\) (–C=O, sydnone), 1664 cm\(^{-1}\) (–C=O, styryl ketone), 1598 cm\(^{-1}\) (–CH=CH), 1347, 1158 cm\(^{-1}\) (–SO2), 827 cm\(^{-1}\) (–C=O); \(^1\)H NMR (DMSO-d\(_6\)): δ 1.67 ppm (t, 3H, CH3), 6.66 ppm (d, 1H, =CH–CO), 7.37 ppm (d, 1H, =CH), 7.58–8.06 ppm (m, 12H, Ar–H), 9.66 ppm (s, 1H, –SO2NH); \(^{13}\)C NMR (DMSO-d\(_6\)): δ 41.62 ppm (CH3), 108.63 ppm (CH=O of chalcone).
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2.2.8.7. 3-(4-Chlorophenyl)-4-((N-(4-(2-amino-4-(4-methoxyphenyl)pyrimidin-5-yl)phenyl)sulfamoyl)-sydnone (8g). Yield 66%. M.p. 154 °C. IR (KBr): 3351 cm⁻¹ (-OH), 2914, 2846 cm⁻¹ (-CH₃), 1773 cm⁻¹ (-C=O, sydnone), 1658 cm⁻¹ (-C=O, styril ketone), 1598 cm⁻¹ (-CH=CH), 1346, 1153 cm⁻¹ (-SO₂), 821 cm⁻¹ (-C=Cl); ¹H NMR (DMSO-d₆): 2.29 ppm (s, 3H, –CH₃), 5.16 ppm (s, 2H, –NH₂), 7.58–8.05 ppm (m, 12H, –Ar-H), 7.78 ppm (s, 1H, –NH₂); ¹³C NMR (DMSO-d₆): 43.44 ppm (CH₃), 198.52 ppm (C=O of sydnone); MS: m/z (rel. int.%) 569 (M⁺)². Anal. (%) for C₂₅H₁₉N₆O₄SCl: C, 56.13; H, 3.58; N, 15.71; Found: C, 56.16; H, 3.54; N, 15.76.

2.2.9. General preparation of the compounds 9a-j

A mixture of freshly prepared solution of sodium ethoxide (2.0 mmol Na in 50 mL ethanol), 8a-j (1.0 mmol) and guanidine nitrate (1.0 mmol) was heated at reflux for 8–12 h. Reaction progress was monitored by TLC (toluene/ethyl acetate, 7:5:2.5). After completion of the reaction the mixture was concentrated under vacuum and remaining material was poured onto crushed ice. The solid produced was separated and stirred for 1 h to maintain pH neutral with dilute acetic acid. The resulting solid was filtered off and washed with cold ethanol, dried and recrystallized from ethanol.

2.2.9.1. 3-(4-Chlorophenyl)-4-((N-(4-(2-amino-4-(3-(4-chlorophenyl)acryloyl)phenyl)sulfamoyl)-sydnone (9a). Yield 62%. M.p. 195 °C. IR (KBr): 3358, 3227 cm⁻¹ (-NH₂), 2917, 2840 cm⁻¹ (-OCH₃), 1749 cm⁻¹ (-C=O, sydnone), 1602 cm⁻¹ (-C=N), 1342, 1151 cm⁻¹ (-SO₂), 828 cm⁻¹ (-C=Cl); ¹H NMR (DMSO-d₆): 6.66 ppm (d, 1H, =CH=CO), 7.40 ppm (d, 1H, =CH), 7.60–8.05 ppm (m, 12H, Ar-H), 9.68 ppm (s, 1H, –SO₂NH); ¹³C NMR (DMSO-d₆): 109.53 ppm (CH of sydnone), 116.67–168.11 ppm (Ar-C), 124.12, 145.57 ppm (CH=CH), 170.56 ppm (C=O of sydnone), 192.43 ppm (C=O of chalcone); MS: m/z (rel. int.%) 515 (M⁺ -1)². Anal. (%) for C₂₇H₂₇N₄O₄SCl: C, 53.50; H, 2.93; N, 8.14; Found: C, 53.43; H, 2.96; N, 8.17.

2.2.9.2. 3-(4-Chlorophenyl)-4-((N-(4-(2-amino-4-p-tolylpyrimidin-5-yl)phenyl)sulfamoyl)-sydnone (9b). Yield 69%. M.p. 221 °C. IR (KBr): 3352, 3224 cm⁻¹ (-NH₂), 2924, 2854 cm⁻¹ (-CH₃), 1749 cm⁻¹ (-C=O, sydnone), 1609 cm⁻¹ (-C=N), 1346, 1158 cm⁻¹ (-SO₂), 827 cm⁻¹ (-C=Cl); ¹H NMR (DMSO-d₆): 6.52 ppm (t, 3H, =CH₂), 7.16 ppm (s, 2H, –NH₂), 7.54–8.27 ppm (m, 12H, Ar-H), 7.78 ppm (s, 1H, pyrimidine-NH), 9.69 ppm (s, 1H, –SO₂NH); ¹³C NMR (DMSO-d₆): 21.36 ppm (CH₃), 109.21 ppm (CH of sydnone), 115.84–159.21 ppm (Ar-C), 124.67, 144.52 ppm (CH=CH), 171.74 ppm (C=O of sydnone), 190.04 ppm (C=O of chalcone); MS: m/z (rel. int.%) 551 (M⁺)². Anal. (%) for C₂₅H₁₉N₆O₄SCl: C, 54.50; H, 3.48; N, 15.25; Found: C, 54.53; H, 3.49; N, 15.22.

2.2.9.3. 3-(4-Chlorophenyl)-4-((N-(4-(2-amino-4-(4-methoxyphenyl)pyrimidin-5-yl)phenyl)sulfamoyl)-sydnone (9c). Yield 81%. M.p. 189 °C. IR (KBr): 3355, 3224 cm⁻¹ (-NH₂), 1749 cm⁻¹ (-C=O, sydnone), 1607 cm⁻¹ (-C=N), 1338, 1157 cm⁻¹ (-SO₂), 823 cm⁻¹ (-C=Cl); ¹H NMR (DMSO-d₆): 5.21 ppm (s, 2H, –NH₂), 7.68–8.02 ppm (m, 12H, Ar-H), 7.82 ppm (1H, pyrimidine-NH), 9.61 ppm (s, 1H, –SO₂NH); ¹³C NMR (DMSO-d₆): 108.64 ppm (CH of sydnone), 112.29–159.15 ppm (Ar-C), 123.18, 143.48 ppm (CH=CH), 163.16 ppm (C=N₂H of pyrimidine), 169.83 ppm (C=O of sydnone); MS: m/z (rel. int.%) 554 (M⁺ -1)². Anal. (%) for C₂₅H₁₉N₆O₄SCl: C, 51.90; H, 2.90; N, 15.13; Found: C, 51.86; H, 2.93; N, 15.15.

2.2.9.4. 3-(4-Chlorophenyl)-4-((N-(4-(2-amino-4-(2-nitrophenyl)pyrimidin-5-yl)phenyl)sulfamoyl)-sydnone (9d). Yield 79%. M.p. 216 °C. IR (KBr): 3348, 3219 cm⁻¹ (-NH₂), 1751 cm⁻¹ (-C=O, sydnone), 1611 cm⁻¹ (-C=N), 1535, 1532 cm⁻¹ (-NO₂), 1340, 1149 cm⁻¹ (-SO₂), 825 cm⁻¹ (-C=Cl); ¹H NMR (DMSO-d₆): 6.58 ppm (d, 1H, =CH=CO), 7.38 ppm (d, 1H, =CH), 7.60–8.07 ppm (m, 12H, Ar-H), 9.67 ppm (s, 1H, –SO₂NH); ¹³C NMR (DMSO-d₆): 43.44 ppm (CH₃), 198.52 ppm (C=O of sydnone); MS: m/z (rel. int.%) 481 (M⁺)². Anal. (%) for C₂₅H₁₉N₆O₄SCl: C, 57.32; H, 3.35; N, 8.72; Found: C, 57.26; H, 3.38; N, 8.70.
(m, 12H, Ar-H), 7.84 ppm (s, 1H, –SO2NH); 13C NMR (DMSO-d6): δ 107.92 ppm (C–NH2 of pyrimidine), 162.25 ppm (C=O of sydnone); MS: m/z (rel. int.%) 556 (M+1)+. Anal. (%) for C28H26N7O5SCl, Calcd: C, 55.31; H, 4.31; N, 16.12; Found: C, 55.37; H, 3.93; N, 17.38.

2.2.9.10. 3-(4-Chlorophenyl)-4-(N-(4-(2-amino-4-phenylpyrimidin-5-yl)phenyl)sulfamoyl)-sydnone (9g). Yield 72%. M.p. 206°C. IR (KBr): 3356, 3227 cm−1 (–NH2), 1747 cm−1 (–C=O, sydnone), 1601 cm−1 (–C=N), 1346, 1151 cm−1 (–SO2), 823 cm−1 (–C=Cl); 1H NMR (DMSO-d6): δ 1.05 ppm (t, 3H, –CH3), 1.62 ppm (CH2), 1.79 ppm (s, 1H, pyrimidine-NH), 7.63–8.29 ppm (m, 12H, Ar-H), 7.82 ppm (s, 1H, pyrimidine-NH), 9.67 ppm (s, 1H, –SO2NH); 13C NMR (DMSO-d6): δ 41.32 ppm (CH3), 108.56 ppm (CH of sydnone), 113.56–158.82 ppm (Ar-C), 123.96, 143.31 ppm (CH=CH), 164.24 ppm (C=O of sydnone), 169.47 ppm (C–NH2 of pyrimidine), 169.47 ppm (C=O of sydnone); MS: m/z (rel. int.%) 537 (M−1)+. Anal. (%) for C24H25N8O2SFC1, Calcd: C, 53.49; H, 3.09; N, 15.69; Found: C, 53.47; H, 2.94; N, 15.50.

2.2.9.11. Biological activity. Antibacterial activity of tested compounds were assessed against micrococcus viz. Staphylococcus aureus (S. aureus), Bacillus subtilis (B. subtilis), Escherichia coli (E. coli), and Pseudomonas aeruginosa (P. aeruginosa) by broth dilution method (Stalons and Thornsberry, 1975). Ciprofloxacin and Metronidazole were used as reference drugs. Antifungal screening data showed that chalcone 8 (4-Cl) possessed excellent activity against Candida albicans. 

2.2.10. Antibacterial activity From screening results, substituted chalcones 8 g (4-Cl) possess very good activity against Gram +ve and Gram –ve bacteria as compared with standard drugs. The remaining chalcones possesses moderate to poor activity against all four bacterial species and the corresponding pyrimidine derivatives, 9b (4-CH3) exhibited very good activity against E. coli, S. aureus, and P. aeruginosa. The remaining pyrimidines displayed moderate to poor activities against all four bacterial species.

2.2.11. Antifungal activity Antifungal screening data showed that chalcone 8e (4-F) exhibit high promising activity against C. albicans. Pyrimidine 9f (4-N(CH3)2) possessed excellent activity against C. albicans. The remaining compounds of the entire series exhibit moderate to poor activity.
3. Conclusions

Our present investigation centers the studies on synthesis, spectral analysis and biological activities of sydnone based chalcone and pyrimidine derivatives. The procedure proved to be more profitable than those previously reported in the literature. Some compounds were found to be very effective as antibacterial and antifungal agents. The presence of chloro/fluoro group at the $p$-position in phenyl ring of chalcone derivatives appears to be electron acceptor group. While the presence of methyl group also present at the $p$-position in phenyl ring of pyrimidine derivatives have reported to be electron donating group which in parts them good biological activity as inferred from structure–activity relationship (SAR) studies.

References


Studies on Synthesis Characterisation and Antimicrobial activity of Pyrimidine based derivatives

Yogesh M. Patel, Kalpesh M. Mehta and Keshav C. Patel*

Department of Chemistry, Veer Narmad South Gujarat University, Surat-395 007, Gujarat, India.

*Corres.author : keshavcpatel@yahoo.com, Tel : (0261)2258384, Fax: (0261) 2258384

Abstract: - m-phenoxy benzaldehydes react with 4-methoxy acetophenone to form chalcone which is treated with thiaourea to form pyrimidine. Pyrimidine react with substituted N-1,3-benzothiazole-2-yl-2-chloro acetamide gives title compounds. The structures of all the synthesized compounds have been confirmed by elemental analysis and spectral data. The synthesized compounds have been tested for their antibacterial activity.

Keywords: Pyrimidine, Benzthiazole, Antimicrobial activity.

INTRODUCTION

Nitrogen and sulphar containing heterocyclic compounds have received considerable attention due to their wide range of pharmacological activity. Pyrimidine and their derivatives are considered to be important for drugs and agricultural chemicals. As pyrimidine is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological activities. The synthesis of substituted pyrimidine and many detailed review have been appeared.

Pyrimidine derivatives possess several interesting biological activities such as antitumor, antiviral, antifungal, anticancer, antibacterial, antinflammatory, analgesic, antagonist, antitriplatelet, antimicrobial, antithrombotic, anti-HIV, antithrombotic, antifilarial, antifolate, antiproliptive activities, etc.

Moreover benzothiazole is other important pharmacodynamic heterocyclic nuclei which when incorporated in different heterocyclic templates have been possess wide spectrum of activities.

The literature study reveals that both pyrimidine and benzthiazole are an important pharmacophor and exhibits out standing biological activities. Encourage by these observation, we synthesized a new series of pyrimidine derivatives by incorporating the benzthiazole moiety in the hope of obtaining better antimicrobial activity agent. All the synthesized compounds have been screened for their antimicrobial activities.

EXPERIMENTAL

General Procedures: Laboratory Chemicals were supplied by Rankem India Ltd. and Ficher Scientific Ltd. Melting points were determined by the open tube capillary method and are uncorrected. The purity of the compounds was monitored by thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene: ethyl acetate (7.5:2.5). The spots were observed by exposure to iodine vapour or by UV light. The IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer (KBr pellets). The 1H-NMR & 13C-NMR spectra were recorded on a Bruker Avance II 400 spectrometer using TMS as the internal standard in CDCl3. Elemental analysis of the newly synthesized compounds were carried out on Carlo Erba 1108 analyzer.
Step-1

\[
\text{Ph-O-Ph + C}_{6}\text{H}_{4}\text{CHO} \xrightarrow{\text{NaOH} \text{CH}_3\text{OH}} \text{Ph-CH=CH-Co}_{6}\text{H}_{4}\text{OCH}_3
\]

\(1\)

\[
\text{NH}_2\text{CSNH}_2/\text{NaOH} \xrightarrow{\text{CH}_3\text{OH}} \text{Ph-Ch=Ch-} \text{Pyrimidine-Ph-OCH}_3
\]

\(2\)

Step-2

\[
\text{ClCH}_2\text{COCl + NH}_2\text{Pyrimidine} \xrightarrow{\text{THF} 0-5\degree\text{C}} \text{Pyrimidine-CO-CH}_3 \xrightarrow{\text{R}} \text{Pyrimidine-R}
\]

\(3a-j\)

Step-3

\[
\text{(2) + (3a-j) \xrightarrow{\text{Acetone/TEA Reflux 3 hrs}} \text{(4a-j)}}
\]

Scheme
Step-1:
Synthesis of 1-(4-methoxyphenyl)-3-(3-phenoxypyphenyl) prop-2-en-1-one (1): To a solution of 3-phenoxyn benzaldehyde (0.01 mol) and 4-methoxyacetophenone (0.01 mol) in ethanol (25 mL) cooled at 5-10 °C was added aqueous sodium hydroxide (70 %, 5mL) drop wise with constant stirring. The reaction mixture was further stirred for 2h and left over night. The reaction mixture was neutralized with concentrated hydrochloric acid, and then the solid separated was collected and crystallized from suitable solvent to get the chalcone derivatives with 80-95 % yield. mp. 178-180 °C, IR (KBr): 1511, 1649, 2840, 2917, 1H NMR (CDCl3) δ ppm; 8.27 (m, 4H,Ar-H); 3.81 (s,3H,-OCH3). Yields 71%, mp. 112-115 °C, IR (KBr): 1369, 1660, 1520, 1745, 745. 1H NMR (CDCl3) δ ppm; 9.46 (s,1H, -NH), 3.78 (s,3H,-OCH3), 4.67 (s,2H,-CH2). Mass (m/z): 226. Anal. (%) for C13H11O2S, Calcd. C, 47.69; H, 3.11; N, 12.36; Found: C, 47.55, H, 3.18, N, 12.43.

Step-2:
General method for the Preparation of N-(1,3-benzothiazole-2-yl)-2-chloroacetamide (3a-j):
In conical flask take 0.01 mole substituted benzothiazole in 25 ml benzene and stirring it for 30 min in ice-bath till temp below 0-5 °C then add drop by drop 0.01 mole chloroacetylene chloride in conical flask within 2h. After complete addition reflux it for 3h then cool it and fall out in ice precipitate come out filter it and recrystallization from alcohol.

Step-3:
General method for synthesis of 2-(4-(4-methoxyphenyl)-6-(3-phenoxypyphenyl) pyrimidin-2-ylthio)-N-(substitutedbenzo[d]thiazol-2-yl) acetamide (4a-j): In R.B.F take 0.01 mole 4-(4-methoxyphenyl)-6-(3-phenoxypyphenyl) pyrimidine-2-thiol in 25ml acetone then add 0.01 mole substituted N-(1,3-benzothiazole-2-yl)-2-chloroacetamide and add 2-3 drop TEA as a catalyst and reflux it for 3h then cool it and fall out in ice precipitate come out filter it and recrystallization from alcohol.

N-(5-chlorobenzo[d]thiazol-2-yl)-2-(4-(4-methoxophenyl)-6-(3-phenoxypyphenyl) pyrimidin-2-ylthio)acetamide (4a). Yield 71%, mp. 112-115 °C, IR (KBr): 3175, 2917, 2840, 1690, 1602, 1530, 745, 695. 1H NMR (CDCl3) δ ppm; 9.45 (s,1H, -NH), 3.78 (s,3H,-OCH3), 4.67 (s,2H,-CH2). Mass (m/z): 610. Anal. (%) for C13H11O2S, Calcd. C, 71.98, H, 5.49; Found: C, 71.95, H, 5.83.

Synthesis of 4-(4-methoxyphenyl)-6-(3-phenoxypyphenyl) pyrimidine-2-thiol (2): A mixture of 1-(4-methoxyphenyl)-3-(3-phenoxypyphenyl)prop-2-en-1-one (0.01 mole), thiourea (0.01 mol) and sodium hydroxide (0.01 mole) in methanol (25 mL) was refluxed for 8h. After the completion of reaction, the resultant mixture was cooled to room temperature. Separated compound was filtered, washed with water, dried and crystallized from methanol get title compound with 80 % yield. mp. 162-164 °C, IR (KBr): 1177, 1625, 2846, 2928, 3345, 181.14. 1H NMR (CDCl3) δ ppm; 8.89 (s,1H, NH), 3.81 (s,3H,-OCH3), 7.08-8.11 (m, 17H,Ar-H). 13C NMR (40 MHz, DMSO-d6): δ 38.15, 55.43, 107.42, 114.98, 115.14, 116.49, 118.31, 118.96, 119.37, 120.39, 121.62, 123.64, 124.25, 125.48, 126.15, 127.74, 128.21, 128.58, 129.28, 130.19, 131.38, 132.83, 136.46, 151.33, 153.70, 159.35, 160.16, 164.71, 165.86, 168.24, 172.63, 173.97. Mass (m/z): 558. Anal. (%) for C13H11N2O2S, Calcd. C, 64.96, H,3.96; N,6.89; Found: C, 64.95, H, 3.93, N, 6.83.

2-(2-(4-(4-methoxyphenyl)-6-(3-phenoxypyphenyl)pyrimidin-2-ylthio)acetamido) benzo[d]thiazole-6-sulfonic acid (4b).
Yield 70%, mp. 201-204 °C, IR (KBr): 3172, 2919, 2845, 1687, 1606, 1533, 1354, 1163, 692. 1H NMR (CDCl3) δ ppm; 9.36 (s,1H, -NH), 3.86 (s,3H,-OCH3), 4.75 (s,2H,-CH2), 7.05-8.46 (m, 17H,Ar-H). 13C NMR (40 MHz, DMSO-d6): δ 36.18, 55.43, 107.42, 114.98, 115.24, 116.74, 118.21, 118.56, 119.84, 120.19, 121.84, 122.14, 123.98, 125.17, 126.32, 127.45, 128.15, 129.86, 130.21, 131.06, 136.22, 140.82, 156.83, 157.04, 159.49, 160.42, 164.53, 165.83, 168.86, 172.30, 174.39. Mass (m/z): 656. Anal. (%) for C13H11N2O2S, Calcd. C, 58.52, H,3.68; N,8.35; Found: C, 58.55, H, 3.63, N, 8.58.
N-(benzol[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-mercapto-3-phenoxyphenyl)pyrimidine-2-ylacetamide (4e). Yield 72%, mp. 204-207 °C, IR (KBr): 3172, 2918, 2842, 1690, 1608, 1537, 695. ¹H NMR (CDCl₃) δ ppm: 9.38 (s, 1H, -NH), 3.83 (s, 3H, OCH₃), 4.57 (s, 2H, CH₂), 7.16-8.52 (m, 18H, Ar-H); ¹³C NMR (40 MHz, DMSO-d₆): δ 37.42, 55.43, 107.48, 114.04, 115.74, 116.13, 118.26, 118.32, 119.65, 120.29, 121.18, 123.42, 124.07, 125.37, 126.73, 127.19, 128.85, 128.29, 129.53, 130.32, 131.54, 132.64, 136.20, 153.17, 157.52, 156.97, 160.01, 164.32, 165.87, 168.42, 172.79, 174.02. Mass (m/z): 576. Anal. (%) for C₂₂H₁₉N₂O₄S₂. Calcd. C, 66.65; H, 4.19; N, 9.72; Found: C, 66.65; H, 4.18; N, 9.78.

N-(6-fluorobenzol[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-mercapto-3-phenoxyphenyl)pyrimidine-2-ylacetamide (4j). Yield 70%, mp. 161-163 °C, IR (KBr): 3172, 2918, 2842, 1690, 1608, 1537, 695. ¹H NMR (CDCl₃) δ ppm: 9.46 (s, 1H, -NH), 3.64 (s, 3H, OCH₃), 4.63 (s, 2H, CH₂), 6.78-8.26 (m, 16H, Ar-H); ¹³C NMR (40 MHz, DMSO-d₆): δ 38.82, 53.43, 107.83, 114.50, 115.99, 116.32, 118.73, 118.63, 119.77, 120.82, 121.54, 123.32, 124.27, 125.28, 126.19, 127.38, 128.37, 128.69, 129.14, 130.63, 131.78, 132.89, 136.17, 143.48, 151.47, 157.02, 159.38, 160.48, 164.88, 165.36, 168.02, 172.81, 174.14. Mass (m/z): 666. Anal. (%) for C₂₂H₁₉N₂O₄S₂. Calcd. C, 57.65; H, 3.33; N, 12.62; Found: C, 57.65; H, 3.38; N, 12.63.
$^1$H NMR (CDCl$_3$) δ ppm: 9.41 (s,1H, NH), 3.70 (s,3H,-OCH$_3$), 4.52 (s,2H,-CH$_2$), 7.06-8.36 (m, 17H,Ar-H); $^{13}$C NMR (40 MHz, DMSO-d$_6$): δ 38.23, 52.47, 105.33, 107.16, 114.59, 115.24, 116.65, 113.98, 118.04, 119.76, 120.13, 123.76, 124.34, 125.14, 126.54, 127.31, 128.56, 128.72, 130.08, 131.43, 132.17, 136.32, 148.87, 157.70, 158.21, 159.39, 160.72, 164.14, 165.64, 168.03, 172.29, 174.83. Mass (m/z): 570. Anal. (%) for C$_{30}$H$_{23}$N$_4$O$_3$S$_2$F, Calcd. C, 63.14; H, 4.06; N, 9.82; Found: C, 63.12; H, 4.08; N, 9.83.

**BIOLOGICAL ACTIVITY**

Minimum inhibitory concentration (MIC) of all the synthesized compounds was determined against four different strains, viz two Gram positive bacteria (S. aureus & S. pyogenes) and two Gram negative bacteria (E. coli & P. aeruginosa) compared with standard drugs ampicillin, chloramphenicol, ciprofloxacin, & norfloxacin by broth dilution method. Antifungal activities against C. albicans and A. niger organisms were compared with standard drugs nystatin and greseofulvin by same method. We have synthesized N-(substituted[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio)acetamide, which showed some of them to have excellent activity against Gram positive and Gram negative bacteria.

**ANTIBACTERIAL ACTIVITY**

From screening results, compounds 4f possesses very good activity against gram +ve and gram –ve bacteria compared with standard drugs. In detail the compounds 4b, 4d and 4e have good activity against E. coli and S.Aureus. Compound 4c & 4h against P.aeruginosa and Compound 4b against S. pyogenus have found good activity. The remaining compounds displayed moderate to poor activities against all four bacterial species.

**ANTIFUNGAL ACTIVITY**

Antifungal screening data showed that Compound 4b & 4h show highly promising activity against C. albicans. Compound 4g possessed excellent activity against A.niger. The remaining compounds of the series exhibited only moderate to poor activity.

**CONCLUSIONS**

Our present investigation is centered on the studies of reactions, synthesis, spectral analysis and biological activities of Pyrimidine based benzthiazole derivatives. The procedure proved more profitable than those previously reported in the literature. Some compounds were found effective as antibacterial and antifungal agents.

<table>
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<th>Comp.</th>
<th>Minimal Bactericidal Concentration ug/ml</th>
<th>Minimal Fungicidal Concentration ug/ml</th>
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<td></td>
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Ampicillin 100 100 250 100 - -
Chloramphenicol 50 50 50 50 - -
Ciprofloxacin 25 25 50 50 - -
Norfloxacin 10 10 10 10 - -
Nystatin - - - - 100 100
Greseofulvin - - - - 500 100
ACKNOWLEDGEMENTS

The authors thank the Professor and Head, Dr. P. Bahadur Department of Chemistry for laboratory facilities, the Librarian of Veer Narmad South Gujarat University, Surat for library facilities and Dhanji Rajani, Microcare Laboratory, Surat, for antimicrobial activity. We also wish to thanks Atul Ltd. for IR spectra, C.D.R.I., Lucknow for elemental analysis, and S.A.I.F., Chandigarh for H NMR and $^{13}$C NMR spectral analysis.

REFERENCES:


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