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ORIGINAL ARTICLE

Synthesis and characterization of novel substituted *N*-benzothiazole-2-yl-acetamides

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Abstract Schiff base derivatives of benzothiazole **2a–e** have been synthesized by reacting with substituted 2-aminobenzothiazole **1a–e** and different substituted benzaldehydes **5a–e**. The obtained Schiff bases reaction with $NaBH_4$ has afforded the corresponding some novel amines **3a–e**. The condensation of amines with chloroacetylchloride leads to novel amide derivatives **4a–e**. The structures of the synthesized compounds are characterized by elemental analysis, IR, MS, ^1H NMR and ^{13}C NMR.

1. Introduction

Various substituted benzothiazoles are known to cover a large domain of pharmacological activities serving as antitumor (Beneteau et al., 1999), anti-microbial (Kabeer et al., 2001; Hassan et al., 1978), anthelmintic (Nadkarni et al., 2000), analgesic (Mruthyunjayasawmy and Shanthaveerappa, 2000), anti-inflammatory (Pontiki and Hadjipavoulou-Litina, 2007; Miyamatsu et al., 1974; Bhusari et al., 2001, 2000a,b) and anticonvulsive (Hays et al., 1994) agents. Moreover, it was reported that the Schiff bases (Hadjipavlou-Litina and Geronikaki, 1998) of thiazole and benzothiazole act as inhibitors of the lipoxygenase affecting inflammation and/or psoriasis. Lipoxygenase is an enzyme which catalyzes the rate-limiting step in the biosynthesis of leukotrienes from arachidonic acid (Brain and Williams, 1990; Muller, 1994). The effective role of azomethine linkage in some biological reactions was also studied (Geronikaki, 1990). Similarly, substituted *N*-benzothiazol-2-yl-amides are an important class of heterocyclic compounds that exhibit a wide range of biological properties such as ubiquitin ligase inhibitors (Parlati et al., 2005), antitumor (Yoshida et al., 2005), antirotavirus infections (Bailey and Pevear, 2004), the adenosine receptor (Alanine et al., 2001; Kerwin et al., 1997) and the nuclear hormone receptor (Kerwin et al., 1997). In particular, some benzothiazoles substituted at the 2-position with a benzoylamino moiety showed antibacterial, antifungal and antitubercular activities (Brade et al., 1998) and it is therefore of interest to consider the synthesis of novel Schiff bases of benzothiazole and amides except **2b–e** and **3d**. The compounds were described in the literature (Rathod et al., 2000; Li et al., 1998; Subramanian et al., 2009; Ojha et al., 2001; Shimidzu and Uno, 1973).

In our previous study, some novel benzothiazole Schiff bases and their reduced amine compounds were determined by UV–vis spectroscopic technique and their acidity constants and pK_a values were evaluated in structure elucidation and

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protonation – deprotonation mechanisms for **2b**, **2d**, **3b**, **3d** (Öğretir et al., 2009). In the present work, we report on (i) the synthesis of a novel benzothiazole Schiff base (ii) reduction of the obtained imines (iii) synthesis of the corresponding amide (iv) spectroscopic characterization of the obtained compounds.

2. Experimental

Melting points (mp) were determined on Gallenkamp apparatus, Infrared (FT-IR) spectra were recorded as pressed KBr disc, using Perkin Elmer Precisely Spectrum 100 FT-IR Spectrophotometer, ^{1}H NMR and ^{13}C NMR spectra were recorded Bruker DPX FT NMR (500 MHz) and (125 MHz) spectrometer instrument at 298 K. Chemical shifts are given in δ (ppm) relative to TMS (DMSO-d_6) as the internal standard. Electron impact mass spectra (EI) were obtained using a (LS/MS-APCl) AGILENT 1100 MSD spectrometer at 100 eV. Elemental analyses were obtained on Elementar Analsensysteme GmbH varioMICRO CHNS (Turkish Technical and Scientific Research Council Laboratories, Ankara, Turkey). TLC was performed on pre-coated silica gel plates (Merk 60, F_{254}, 0.25 mm). Organic solvents used were of HPLC grade or were purified by the standard procedure. All reagents were of commercial quality or were purified before use.

*2.1. General procedure for the synthesis of Schiff's Bases **2a–e** (Vicini et al., 2003)*

A solution of 2-amino-6-methyl benzothiazole (**1a**, 10 g, 61 mmol) and *m*-hydroxy benzaldehyde (**5a**, 7.45 g, 61 mmol) in methanol (100 ml) was refluxed for 2 h. The mixture was left to stand at room temperature overnight and then concentrated. The residue was washed with *n*-hexane (2×100 ml) and filtered off. The residue was hydrolyzed in water and extracted with EtOAc (4×50 ml). After drying in Na_2SO_4 and evaporation, the crude product (**2a**, 12.5 g, 76%) was obtained then recrystallized from CH_2Cl_2. Compounds **2b–e** were prepared using the same method described above.

*2.1.1. 3-{[(6-Methyl-1,3-benzothiazol-2-yl)imino]methyl}phenol **2a***

Yield:12.5 g (76%) mp 212–214 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.40 (s, 3H, CH_3-Benzothiazole), 7.06 (dd, J = 7.9 Hz, 1H, H13), 7.33 (dd, J = 8.26 Hz, 1H, H15), 7.40 (t, J = 7.84 Hz, 1H, H14), 7.49 (s, 1H, H11), 7.50 (d, J = 8.56 Hz, 1H, H4), 7.82 (d, J = 8.28 Hz, 1H, H5), 7.84 (s, 1H, H7), 9.10 (s, 1H, –CH═N–), 9.90 (br s, 1H, Ar-OH). ^{13}C NMR (DMSO-d_6 125 MHz): δ 21.58, 117.88, 121.53, 122.37, 122.69, 128.54, 130.72, 134.62, 135.53, 136.32, 149.84, 158.35, 167.54, 170.76, 193.59 ppm. MS (EI): m/z (%) = 269.1 ($M^+ + 1$, 21.5), 271.1 (2.5), 165.0 (100), 137.1 (45). Anal. Calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44; S, 11.95. Found: C, 67.28; H, 4.67; N, 10.52; S, 11,35. IR ν_{max} 3300, 3045, 3040, 1605, 1597, 1530, 1505 cm^{-1}.

*2.1.2. 2-{[(4-Methyl-1,3-benzothiazol-2-yl)imino]methyl}phenol **2b***

Yield: 14.31 g (88%) mp 160–162 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.65 (s, 3H, CH_3-Benzothiazole), 7.01 (d, J = 7.42 Hz, 1H, H12), 7.04 (t, J = 8.20 Hz, 1H, H6), 7.31 (d, J = 7.39 Hz, 1H, H5), 7.33 (d, J = 8.77 Hz, 1H, H7), 7.52 (dt, J = 8.44 Hz, 1H, H13), 7.87 (t, J = .8.56 Hz, 1H, H14), 7.94 (dd, J = 7.80 Hz, 1H, H15), 9.4 (s, 1H, –CH═N–), 11.80 (br s, 1H, Ar-OH). ^{13}C NMR (DMSO-d_6 125 MHz): δ 18.55, 117.42, 120.13, 120.19, 120.32, 125.80, 127.58, 131.47, 132.72, 134.07, 136.04, 150.94, 160.94, 166.08, 169.73 ppm. MS (EI): m/z (%) = 269.1 ($M^+ + 1$, 8.7), 241.1 (6.5), 179.1 (5.2), 165.1 (100), 137.1 (6.5). Anal. Calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44; S, 11.95. Found: C, 67.04; H, 4.08; N, 10.52; S, 11.46. IR ν_{max} 3373, 1604, 1597, 1551 cm^{-1}.

*2.1.3. 6-Methyl-N-[(4-methylphenyl)methylidene]-1,3-benzothiazol-2-amine **2c***

Yield: 11.68 g (72%) mp 146–147 °C. (DMSO-d_6, 500 MHz): δ 2.43 (s, 3H, Ar-CH_3), 2.46 (s, 3H, CH_3-Benzothiazole), 7.34 (dd, J = 7.59 Hz, 1H, H5), 7.42 (d, J = 7.99 Hz, 2H, H12, H14), 7.82 (d, J = 8.28 Hz, 1H, H4), 7.87 (s, 1H, H7), 8.00 (d, J = 8.07 Hz, 2H, H11, H15), 9.14 (s, 1H, –CH═N–). ^{13}C NMR (DMSO-d_6 125 MHz); δ 21.57, 21.88, 122.36, 122.63, 128.50, 130.30, 130.59, 132.50, 134.59, 135.43, 144.58, 149.85, 167.20, 170.95 ppm. Anal. Calcd for $C_{16}H_{14}N_2S$: C, 72.15; H, 5.30; N, 10.52; S, 12.04. Found: C, 72.01; H, 5.40; N, 10.36; S, 11.98. IR ν_{max} 1607, 1589, 1556 cm^{-1}.

*2.1.4. 2-[(1,3-Benzothiazol-2-ylimino)methyl]phenol **2d***

Yield: 13.26 g (85%) mp 149–151 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.77 (t, J = 7.35 Hz, 1H, H5), 6.83 (d, J = 7.93 Hz, 1H, H12), 7.02 (t, J = 7.53 Hz, 1H, H13), 7.1 (t, J = 7.36 Hz, 1H, H14), 7.21 (t, J = 7.19 Hz, 1H, H6), 7.23 (d, J = 7.29 Hz, 1H, H4), 7.38 (d, J = 7.91 Hz, 1H, H7), 7.66 (d, J = 7.71 Hz, 1H, H15), 9.05 (s, 1H, –CH═N–), 11.50 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6 125 MHz): δ 117.44, 120.09, 120.33, 122.89, 123.07, 125.78, 127.20, 131.54, 134.43, 136.15, 151.70, 161.05, 166.33, 170.91 ppm. MS (EI): m/z (%) = 255.1 ($M^+ + 1$, 24.2), 209.0 (23.9), 177.0 (23.2), 151.0 (100), 137.1 (11.5). Anal. Calcd for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96; N, 11.02; S, 12.61. Found: C, 66.10; H, 3.90; N, 11.03; S, 12.59. IR ν_{max} 3437, 1609, 1572, 1505 cm^{-1}.

*2.1.5. N-[(4-methoxyphenyl)methylidene]-6-methyl-1,3-benzothiazol-2-amine **2e***

Yield: 10.1 g (65%) mp 132–133 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.45 (s, 3H, CH_3-Benzothiazole), 3.89 (s, 3H, Ar-OCH_3), 7.15 (d, J = 8.85 Hz, 2H, H12, H14), 7.33 (d, J = 8.55 Hz, 1H, H5), 7.80 (d, J = 8.25 Hz, 1H, H4), 7.84 (s, 1H, H7), 8.06 (d, J = 8.75 Hz, 2H, H11, H15), 9.09 (s, 1H, –CH═N–). ^{13}C NMR (DMSO-d_6 125 MHz): δ 21.56, 56.14, 115.23, 122.31, 122.47, 127.84, 128.41, 132.74, 134.45, 135.22, 149.89, 164.12, 166.48, 171.19 ppm. Anal. Calcd for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92; S, 1136. Found: C, 68.1; H, 4.97; N, 9.98; S, 10.98. IR ν_{max} 1600, 1569, 1466 cm^{-1}.

*2.2. General procedure for the synthesis of substituted 1,3-benzothiazole-2-yl phenyl methyl amine **3a–e** (Billman and Diesing, 1957)*

3-{[(6-Methyl-1,3-benzothiazol-2-yl)imino]methyl}phenol (**2a**, 6 g, 22.3 mmol) were dissolved in methanol $NaBH_4$ was added to the stirred solution at room temperature until the yellow color of the Schiff bases disappeared. Cold water was added to the solution to precipitate the compounds. The precipitates were recrystallized from methanol to obtain compound **3a**

(5.529 g, 92%). Compounds **3b–e** were prepared using the same method described above.

2.2.1. 3-{[(6-Methyl-1,3-benzothiazol-2-yl)amino] methyl}phenol ***3a***

Yield: 5.52 g (92%) mp 169–171 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.32 (s, 3H, CH_3-benzothiazole), 4.50 (d, J = 5.60 Hz, 2H, Ar-CH_2N), 6.65 (d, J = 7.22 Hz, 1H, H15), 6.79 (s, 1H, H11, d, J = 6.08 Hz, 1H, H13), 7.02 (d, J = 8.13 Hz, 1H, H5), 7.14 (t, J = 7.98 Hz, 1H, H14), 7.28 (d, J = 8.12 Hz, 1H, H4), 7.46 (s, 1H, H7), 8.35 (t, J = 5.62 Hz, 1H, NH-benzothiazole), 9.4 (br s, 1H, Ar-OH). ^{13}C NMR (DMSO-d_6 125 MHz): δ 21.22, 47.60, 114.40, 114.56, 118.20, 118.36, 121.35, 127.01, 129.80, 130.50, 130.95, 140.93, 150.81, 157.91, 166.04 ppm. MS (EI): m/z (%) = 272.1 ($M^+ + 2$, 17.9), 271.1 ($M^+ + 1$, 100), 107.1 (11.2). Anal. Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found: C, 66.62; H, 5.20; N, 10.34; S, 11.82. IR ν_{max} 3520, 3412, 1594, 1571 cm^{-1}.

2.2.2. 2-{[(4-Methyl-1,3-benzothiazol-2-yl)amino] methyl}phenol ***3b***

Yield: 5.61 g (93%) mp 199–200 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.46 (s, 3H, CH_3-benzothiazole), 4.52 (d, J = 5.72 Hz, 2H, Ar-CH_2N), 6.79 (dt, J = 7.39 Hz, 1H, H14), 6.84 (dd, J = 8.06 Hz, 1H, H12), 6.93 (t, J = 7.40 Hz, 1H, H13), 7.06 (d, J = 7.40 Hz, 1H, H15), 7.11 (dt, J = 7.69 Hz, 1H, H6), 7.27 (dd, J = 7.52 Hz, 1H, H5), 7.47 (d, J = 7.75 Hz, 1H, H7), 8.45 (t, J = 5.79 Hz, 1H, NH-benzothiazole), 10.00 (br s, 1H, Ar-OH). ^{13}C NMR (DMSO-d_6 125 MHz): δ 18.62 43.32, 116.08, 118.93, 119.42, 121.39, 125.34, 126.83, 127.49, 128.87, 129.90, 130.09, 151.27, 155.71, 166.50 ppm.. MS (EI): m/z (%) = 272.1 ($M^+ + 2$, 11.3), 271.1 ($M^+ + 1$, 73.2), 165.00 (100.0), 107.1 (9.4). Anal. Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found: C, 66.01; H, 5.02; N, 10.15; S, 11.78. IR ν_{max} 3525, 3430, 1602, 1594 cm^{-1}.

2.2.3. 6-Methyl-N-(4-methylbenzyl)-1,3-benzothiazol-2-amine ***3c***

Yield: 5.01 g (83%) mp 203–204 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.20 (s, 3H, Ar-CH_3), 2.40 (s, 3H, CH_3-benzothiazole), 4.51 (d, J = 5.73 Hz, 2H, Ar-CH_2N), 7.03 (d, J = 7.40 Hz, 1H, H5), 7.17 (d, J = 7.80 Hz, 2H, H12, H14), 7.27 (d, J = 8.05 Hz, 3H, H11, H15 and H4), 7.48 (s, 1H, H7), 8.34 (t, J = 5.72 Hz, 1H, NH-benzothiazole). ^{13}C NMR (DMSO-d_6 125 MHz): δ 21.15, 21.22, 47.45, 118.20, 121.34, 127.00, 127.86, 129.37, 130.50, 130.94, 136.42, 136.55, 150.81 165.97 ppm. Anal. Calcd for $C_{16}H_{16}N_2S$: C, 71.60; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.59; H, 5.99; N, 10.45; S, 11.92. IR ν_{max} 3330, 1602, 1595 cm^{-1}.

2.2.4. 2-[(1,3-Benzothiazol-2-ylamino)methyl]phenol ***3d***

Yield: 5.56 g (92%) mp 181–182 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.51 (s, 2H, Ar-CH_2N), 6.77 (t, J = 7.30 Hz, 1H, H5), 6.83 (d, J = 7.93 Hz, 1H, H6), 7.02 (d, J = 7.53 Hz, 1H, H12), 7.10 (t, J = 7.36 Hz, 1H, H13), 7.21 (t, J = 7.19 Hz, 1H, H14), 7.23 (d, J = 7.29 Hz, 1H, H4), 7.38 (d, J = 7.91 Hz, 1H, H7), 7.66 (d, J = 7.71 Hz, 1H, H15), 8.40 (s, 1H, NH-benzothiazole). ^{13}C NMR (DMSO-d_6 125 MHz): δ 43.14, 115.79, 118.34, 119.37, 121.42, 121.44, 125.22, 126,03, 128.69, 129.29, 130.75, 152.64, 155.61, 166.92 ppm. MS (EI): m/z (%) = 256.0.(M^+, 16), 257.1 (100), 151.0 (80), 107.1 (2.5). Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93; S, 12.51. Found: C, 65.61; H, 4.70; N, 10.95; S, 12.49. IR ν_{max} 3416, 1594, 1571, 1551 cm^{-1}.

2.2.5. N-(4-methoxybenzyl)-6-methyl-1,3-benzothiazol-2-amine ***3e***

Yield: 4.41 g (73%) mp 175–176 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.3 (s, 3H, Ar-CH_3), 3.75 (s, 3H, CH_3-benzothiazol), 4.50 (d, 2H, J = 5.63 Hz, Ar-CH_2), 6.91 (d, J = 8.64 Hz, 2H, H12, H14), 7.03 (d, J = 8.12 Hz, 1H, H5), 7.27 (d, J = 8.11 Hz, 1H, H4), 7.31 (d, J = 8.60 Hz, 2H, H11, H15), 7.46 (s, 1H, H7), 8.31 (t, 1H, J = 5.63 Hz, NH-benzothiazole). ^{13}C NMR (DMSO-d_6 125 MHz): δ 21.72, 47.19, 55.54, 114.23, 118.19, 121.34, 126.99, 129.27, 130.48, 130.92, 131.34, 150.82, 158.86, 165.92 ppm. Anal. Calcd for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85; S, 11.28. Found: C, 67.55; H, 5.65; N, 9.83; S, 11.31. IR ν_{max} 3420, 1600, 1570 cm^{-1}.

2.3. General procedure for the synthesis of the substituted N-benzothiazole-2-yl-amides ***4a–e*** *(Davion et al., 2004)*

To a mixture of the amine compound (**3a**, 5.00 g, 18.49 mmol) and triethylamine (1 ml, 7.10 mmol) in dry dichloromethane (DCM) (50 ml) was added chloroacetyl chloride (4.41 ml, 55.47 mmol). The reaction mixture was heated to reflux for 1 h. After cooling, the precipitated product was filtered off. The crude residue was heated, hydrolyzed in water (10 ml) and extracted with dichloromethane (5 × 10 ml). After drying ($MgSO_4$) and evaporation, crystalline was obtained (**4a**, 6.3 g, 80%), which was recrystallized from chloroform. Compounds **4b–e** were prepared using the same method described above.

2.3.1. 3-{[(Chloroacetyl)(6-methyl-1,3-benzothiazol-2-yl)amino]methyl}phenyl chloroacetate ***4a***

Yield: 6.3 g (80%) mp 157–158 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.45 (s, 3H, CH_3-benzothiazole), 4.65 (s, 2H, Ar-CH_2N), 4.75 (s, 2H, O(CO)CH_2Cl), 5.51 (s, 2H, N(CO)CH_2Cl), 7.10 (s, 1H, H7), 7.12 (d, J = 8.42 Hz, 1H, H4), 7.21 (d, J = 7.66 Hz, 1H, H13), 7.27 (d, J = 8.27 Hz, 1H, H5), 7.48 (t, J = 7.71 Hz, 1H, H14), 7.68 (d, J = 8.11 Hz, 1H, H15), 7.83 (s, 1H, H11). MS (EI): m/z (%) = 423.00 (M^+, 7.9), 349.00 (59.3), 347.00 (100), 285.1 (32.1), 107.1 (8.4). Anal. Calcd for $C_{19}H_{16}Cl_2N_2O_3S$: C, 53.90; H, 3.81; N, 6.62; S, 7.58. Found: C, 53.92; H, 3.80; N, 6.60; S, 7.57. IR ν_{max} 1780, 1672, 1610, 1505 cm^{-1}.

2.3.2. 2-{[(Chloroacetyl)(4-methyl-1,3-benzothiazol-2-yl)amino]methyl}phenyl chloroacetate ***4b***

Yield: 5.01 g (64%) mp 139–140 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.45 (s, 3H, CH_3-benzothiazole), 4.73 (s, 2H, Ar-CH_2N), 4.76 (s, 2H, O(CO)CH_2Cl), 5.53 (s, 2H, N(CO)CH_2Cl), 7.16 (d, J = 7.66 Hz, 1H, H12), 7.23–7.32 (m, 4H, H13, H14, H5 and H7), 7.39 (br t, J = 7.68 Hz, 1H, H15), 7.83 (br t, J = 4.26 Hz, 1H, H6). MS (EI): m/z (%) = 424.00 ($M^+ + 1$, 6.4), 347 (60.9), 241.00 (100.0), 105.1 (3.9). Anal. Calcd for $C_{19}H_{16}Cl_2N_2O_3S$: C, 53.90; H, 3.81; N, 6.62; S, 7.58. Found: C, 53.90; H, 3.82; N, 6.61; S, 7.57. IR ν_{max} 1715, 1700, 1624, 1582, cm^{-1}.

2.3.3. 2-Chloro-N-(6-methyl-1,3-benzothiazol-2-yl)-N-(4-methylbenzyl)acetamide ***4c***

Yield: 4.5 g (70%) mp 164–165 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.27 (s, 3H, Ar-CH_3), 2.43 (s, 3H, CH_3-benzothiazole), 4.75 (s, 2H, Ar-CH_2N), 5.55 (s, 2H, N(CO)CH_2Cl), 7.14 (d, J = 8.54 Hz, 2H, H12, H14), 7.17 (d, J = 8.52 Hz, 2H, H11, H15), 7.27 (d, J = 8.24 Hz, 1H, H5), 7.66 (d, J = 8.26 Hz, 1H, H4), 7.83 (br s, 1H, H7). ^{13}C NMR (DMSO-d_6 125 MHz): δ 21.10, 21.50, 43.96, 50.16, 121.35, 121.67, 126.59, 128.14, 129.35, 133,30, 133.57, 134.31, 137.15, 145.96, 159,01, 167.72 ppm. MS (EI): m/z (%) = 346.1 ($M^+ + 1$, 17.20), 345.1 (M^+, 100), 269.1 (35.00), 105.1 (43.25). Anal. Calcd for $C_{18}H_{17}ClN_2OS$: C, 62.69; H, 4.97; N, 8.12; S, 9.30. Found: C, 62.67; H, 4.89; N, 8.02; S, 9.23. IR ν_{max} 1689, 1602, 1505 cm^{-1}.

2.3.4. 2-{[1,3-Benzothiazol-2-yl(chloroacetyl)amino]methyl}phenyl chloroacetate ***4d***

Yield: 7.87 g (82%) mp 137–139 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.70 (s, 2H, Ar-CH_2N), 4.80 (s, 2H, O(CO)CH_2Cl), 5.55 (s, 2H, N(CO)CH_2Cl), 7.08 (d, J = 7.61 Hz, 1H, H12), 7.24 (dt, J = 7.28 Hz, 1H, H6), 7.31 (dd, J = 7.28 Hz, 1H, H4), 7.38 (t, J = 8.47 Hz, 2H, H13 and H14), 7.45 (dt, J = 7.65 Hz 1H, H5), 7.76 (dd, J = 8.06 Hz, 1H, H7), 8.05 (d, J = 7.66 Hz, 1H, H15). MS (EI): m/z (%) = 410.0 (M^+, 21.9), 409.00 (100.0), 333.0 (3.5), 183.00 (94.1), 107.1 (23.8). Anal. Calcd for $C_{18}H_{14}Cl_2N_2O_3S$: C, 52.82; H, 3.45; N, 6.84; S, 7.83. Found: C, 52.80; H, 3.44; N, 6.80; S, 7.85. IR ν_{max} 1758, 1699, 1611, 1563, 1502 cm^{-1}.

2.3.5. 2-Chloro-N-(4-methoxybenzyl)-N-(6-methyl-1,3-benzothiazol-2-yl)acetamide ***4e***

Yield: 6.09 g (80%) mp 162–163 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.40 (s, 3H, CH_3-benzothiazole), 3.70 (s, 3H, Ar-OCH_3), 4.75 (s, 2H, Ar-CH_2N), 5.51 (s, 2H, N(CO)CH_2Cl), 6.92 (d, J = 8.59 Hz, 2H, H12, H14), 7.21 (d, J = 8.55 Hz, 2H, H11, H15), 7.28 (d, J = 8.24 Hz, 1H, H5), 7.68 (d, J = 8.25 Hz, 1H, H4), 7.83 (s, 1H, H7). ^{13}C NMR (DMSO-d_6 125 MHz): δ 21.50, 44.00, 49.88, 55.54, 114.70, 121.12, 121.35, 121.59, 121.67, 128.42, 133.30, 134.31, 145.97, 159.10, 167.71 ppm. Anal. Calcd for $C_{18}H_{17}ClN_2O_2S$: C, 59.91; H, 4.75; N, 7.76; S, 8.89. Found: C, 59.83; H, 4.65; N, 7.75; S, 8.82. IR ν_{max} 1701, 1615, 1582, 1515 cm^{-1}.

3. Results and discussion

The title compounds, **2a**–**4e** have been synthesized according to the described process in Scheme 1. The structures of all the compounds **2a–4e** were established on the basis of elemental analyses, IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data.

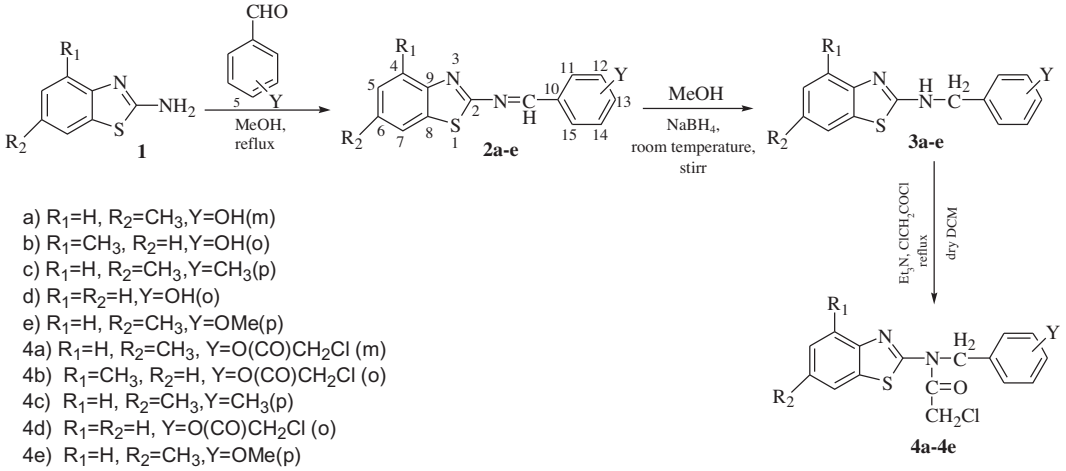
The novel Schiff base **2a** was synthesized according to Scheme 1. The products **2b** and **2e** compounds which were formed through the condensation of aldehyde with amines and **3d** were literature compounds (Rathod et al., 2000; Li et al., 1998; Subramanian et al., 2009; Ojha et al., 2001 and Shimidzu and Uno, 1973). Compounds **2a**, **2c** and **2d** were formed through the condensation of aldehyde with amines in good yields (76, 72 and 85%). The IR spectra of benzothiazole Schiff base **2a–e** exhibit one characteristic band within the range of 1605–1615 cm^{-1}, which can be assigned as (–CH═N–). The existence of the aromatic rings is proved by the following bands: aromatic carbon-H stretching υC–H (3045–3040 cm^{-1}), phenyl ring stretching υC–C (1597, 1530, 1505 cm^{-1}).

In the ^{1}H NMR spectra of benzothiazole Schiff bases, the chemical shift of the aromatic protons is observed within the 7.01–8.06 ppm region of spectrum. The hydroxyl protons for **2a, 2b** and **2d** appear as a broad signal within the 9.90–11.80 ppm. A sharp singlet is observed within the 9.05–9.14 ppm region of spectrum, which corresponds to the azomethine proton.

Furthermore, in the ^{13}C NMR spectrum, a down field shift in peak positions is observed at δ 167.54 ppm due to the presence of carbon atom which is double bonded to nitrogen atoms. The EI-MS of **2a**, **2b** and **2d** show strong molecular ion peaks (m/z 269.1, 15.5%), (m/z 269.1, 10.5%), (m/z 254.1, 10%), respectively. This suggests that the reaction of substituted 2-aminobenzothiazole with different substituted benzaldehydes produces exclusively the Schiff bases. These data confirm the proposed stoichiometry and the structure.

The reduction of benzothiazole Schiff bases **2a–e** by $NaBH_4$ in methanol afforded the corresponding amine compounds **3a–e** in good yields 73–93% (Scheme 1). IR studies of each amine compound confirm the formation of –NH– groups, which are observed in the range of 3350–3437 cm^{-1}. The spectra of compounds **3a** and **3b** having free OH groups display somewhat broadened bands within the 3420–3425 cm^{-1} region. The integral intensities of each signal in the ^{1}H NMR spectra of the amine compounds are found to agree with the number of different types of protons present. The ^{1}H NMR spectra of the compounds **3a–e** revealed a fine triplet at δ 8.31–8.45 ppm for the –NH– group. The signals of the methylene protons for the –CH_2–NH– group were detected in the region expected in the range of δ 4.50–4.52 ppm as a doublet. The spectra of **3a** and **3b** show a singlet at δ 9.4 and δ 10.0 ppm due to the hydrogen of the hydroxyl group. In the ^{1}H NMR spectra of compound **3a**, the peaks at 6.65 ppm (d, 1H), 6.79 ppm (s, d, 2H), 7.02 ppm (d, 1H), 7.14 ppm (t, 1H), 7.28 ppm (d, 1H) and 7.46 ppm (s, 1H) are assigned to be H15, H11, H13, H5, H14, H4, H17, respectively, as aromatic protons. Aromatic protons of compounds **3b–e** show similar characteristics as those discussed in compound **3a**. In the mass spectral pattern of compound **3a** and **3d**, the base peak is the $M^+ + 1$ (m/z 271.1, 100%), $M^+ + 1$ (m/z 257.1, 100%), respectively.

The substituted amine compounds **3a–e** were reacted with chloroacetyl chloride in dichloromethane to provide the corresponding amide **4c, 4e** and esters in good yield **4a**, **4b** and **4d** 60–80% (Scheme 1). The IR spectra of the ester products depict ν(–N–C═O) bands within the range of 1672–1699 cm^{-1} and ν(OC═O) bands at 1715–1780 cm^{-1}, which support the assigned structure **4a**, **4b** and **4d**. In the IR spectra of the obtained amides **4c** and **4e**, carbonyl amide absorption bands appeared to be at 1689–1701 cm^{-1}. Spectral studies reveal that the amide possesses mono carbonyl group. In the ^{1}H NMR spectra of the ester compound **4a** the three different methylene protons of the newly synthesized esters were detected to appear as three separate singlets at 4.65, 4.75 and 5.51 ppm as expected for ester compounds. The seven aromatic protons of the ester compound **4a** appear as four doublets, two singlets and a triplet. These doublets appear at chemical shift values of 7.12–7.21 ppm corresponding to H4 and H13, and 7.27–7.68 ppm for H5 and H15. Two singlets are observed within the 7.10–7.83 ppm region of spectrum, which corresponds to H7 and



Scheme 1 Reaction pathways for synthesis of **2a–4e**.

H11. A triplet appears at 7.48 ppm, which is assigned as H14. In the ^{1}H NMR spectra of the amide compound **4c** the two different methylene protons appear as two separate singlets at 4.75 and 5.55 ppm. Aromatic protons of compound **4c** show similar characteristics as those discussed in compound **4a**. In the ^{13}C NMR spectrum of **4c**, peak at 167.72 corresponds to carbonyl carbon and peaks at 21.10, 21.50, 43.96 and 50.16 indicate the presence of methyl and methylene carbons, respectively, in the structure. The EI-MS of **4b** registered a molecular ion peak at (*m*/*z* 424, 10%) ($M^+ + 1$) and fragment ions at (*m*/*z* 347, 60.9%), (*m*/*z* 105, 3.9%) and the base peak at (*m*/*z* 241, 100%) well attests our assignment. The mass spectrum of **4c** showed a molecular ion peak at (*m*/*z* 346.1, 15%) ($M^+ + 1$). The base peak observed at *m*/*z* 345.1 and other fragmentations confirmed our assignment. Along with the above spectral methods, the interesting mass fragmentation study has also helped to confirm the structure of the compounds **2a–4e**.

As a result we can conclude that the suggested formulae were confirmed by spectroscopy.

4. Conclusion

Unlike other studies in the literature (Vicini et al., 2003; Billman and Diesing, 1957; Davion et al., 2004), the compounds of **2a** and **4e** were synthesized according to the references given but by realising some modifications such as in reaction time, solvent type and atmospheric pressure a decrease in reaction time was obtained and an increase in reaction yield. Additionally the solvent used is not greately hazardous for the environment and this also means an important benefit of our method. All spectroscopic analyses confirmed the proposed structures of these compounds.

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