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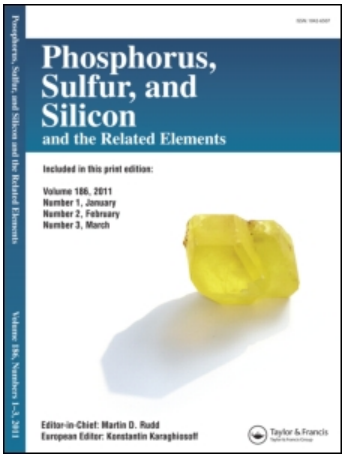

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Synthesis of 3-[4-(1-Benzofuran-2-yl)-1,3-thiazol-2-yl]-2-(4-aryl)-1,3-thiazolidin-4-one Derivatives as Biological Agents

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SYNTHESIS OF 3-[4-(1-BENZOFURAN-2-YL)-1,3-THIAZOL-2-YL]-2-(4-ARYL)-1,3-THIAZOLIDIN-4-ONE DERIVATIVES AS BIOLOGICAL AGENTS

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A protocol for the synthesis of 3-[4-(1-benzofuran-2-yl)-1,3-thiazol-2-yl]-2-(4-aryl)-1,3-thiazolidin-4-one derivatives (5a–e) has been developed from 1-(1-benzofuran-2-yl)-2-bromoethanone (2),which served as a key intermediate for the synthesis of the title compounds. The reaction of compound 2 with thiourea furnished 4-(1-benzofuran-2-yl)-1,3-thiazol-2-amine 3, which upon further reaction with various aromatic aldehydes, gave Schiff bases 4a–e. These Schiff bases, when treated with thioacetic acid in the presence of catalytic amount of anhydrous $ZnCl_2$, yielded thiazolidinone derivatives 5a–e. All the newly synthesized compounds have been characterized by analytical and spectral data and screened for their antimicrobial and analgesic activity.

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Keywords Analgesic and antimicrobial activity; anhydrous $ZnCl_2$; 1-(1-benzofuran-2-yl)-2-bromoethanone; Schiff base; thiazolidinone ring; thioacetic acid.

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INTRODUCTION

The structural and therapeutic diversity coupled with commercial viability of small heterocyclic molecules has fascinated organic and medicinal chemists. Benzo[b]furan derivatives are an important class of organic compounds, which are known to be present in many natural products[1] and possess physiological activity. They have found applications in agrochemicals,[2,3] pharmaceuticals,[4–10] and cosmetics.[11] Benzo[b]furans are building blocks of optical brighteners.[12] Many natural benzo[b]furans have physiological, pharmacological, and toxic properties, and as a result, there is continuing interest in their chemical synthesis. Cyclization reactions of various types have been used to produce substituted benzo[b]furans.[13,15] In recent years, 4-thiazolidinones and oxazolidinones are the most

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extensive investigated class of compounds, which have many interesting activity profiles, namely antibiotics represented by linezolod, COX-1 inhibitors, inhibitors of the bacterial enzyme Mur B, non-nucleoside inhibitors of HIV-RT, and antihistaminic agents.[16–21] Consequently, many different protocols have been developed that allow for the synthesis of 4-thiazolidinone skeletons. Along with this, a vast amount of literature is available describing a wide range of biological activity of thiazolidinone derivatives.[22–24] Thus with an effort to capitalize the pharmacological potential of the 4-thiazolidinone nucleus and to improve the efficiency, output, and quality of the process, the present investigation deals with the synthesis, characterization, and biological studies of some new 3-[4-(1-benzofuran-2-yl)-1,3-thiazol-2-yl]-2-(4-aryl)-1,3-thiazolidin-4-one derivatives.

RESULTS AND DISCUSSION

The experiments were directed towards the coupling-cyclization of 1-(1-benzofuran-2-yl)-2-bromoethanone[25] with thiourea in absolute ethanol to form 4-(1-benzofuran-2-yl)-1,3-thiazol-2-amine.[26] The synthesis of 4-(1-benzofuran-2-yl)-1,3-thiazol-2-amine **3** by the conventional method is preferred over the microwave-assisted method[26] when compared to the yield obtained. The condensation of 4-(1-benzofuran-2-yl)-1,3-thiazol-2-amine **3** with different aromatic aldehydes furnished the Schiff bases (**4a–e**), which upon further reaction with thioacetic acid in a catalytic amount of anhydrous $ZnCl_2$, gave 1,3-thiazolidin-4-one derivatives (**5a–e**) with excellent yield. The formation of Schiff bases (**4a–e**) were confirmed from IR, NMR, and mass spectral data. In the IR spectrum, the absence of an absorption band due to NH_2 group around 3342 cm^{-1} and the presence of an absorption band at 1620 cm^{-1} due to C=N group confirmed the formation of Schiff bases. The ^1H NMR spectrum of compound **4a** displayed a singlet at δ 2.53 due to HC=N proton, another singlet at δ 6.89 due to CH proton of thiazole ring, and a multiplet between δ 7.36–8.07due to the 10 aromatic protons. The absence of a singlet around δ 4.35 ppm due to NH_2 confirmed the formation of Schiff base **4a**. The IR spectrum of compound **5a** showed absorption band at 1678 cm^{-1} due to C=O. ^1H NMR spectrum of compound **5a** showed a singlet at δ 3.85 due to methylene protons of the thiazolidinone ring and another singlet at δ 7.28 due to the methine proton of the thiazole ring. It also displayed a singlet at δ 4.18 due to the methine proton of the thiazolidinone ring and a multiplet between δ 7.21–7.98 due to 10 aromatic protons. The spectral data revealed the formation of the 1,3-thiazolidin-4-one ring (Scheme 1).

BIOLOGICAL STUDIES

Antimicrobial Activity

The newly synthesized compounds were screened for antimicrobial activity by the cup plate method.[27] The in vitro antimicrobial activity was carried out using four bacteria and four fungal organisms. (See the Supplemental Materials, available online, for complete details.)

Analgesic Activity

Analgesic activity to newly synthesized compounds was carried out using adult Swiss albino mice (six animals per group) by abdominal constriction method.[28] (See the Supplemental Materials.)

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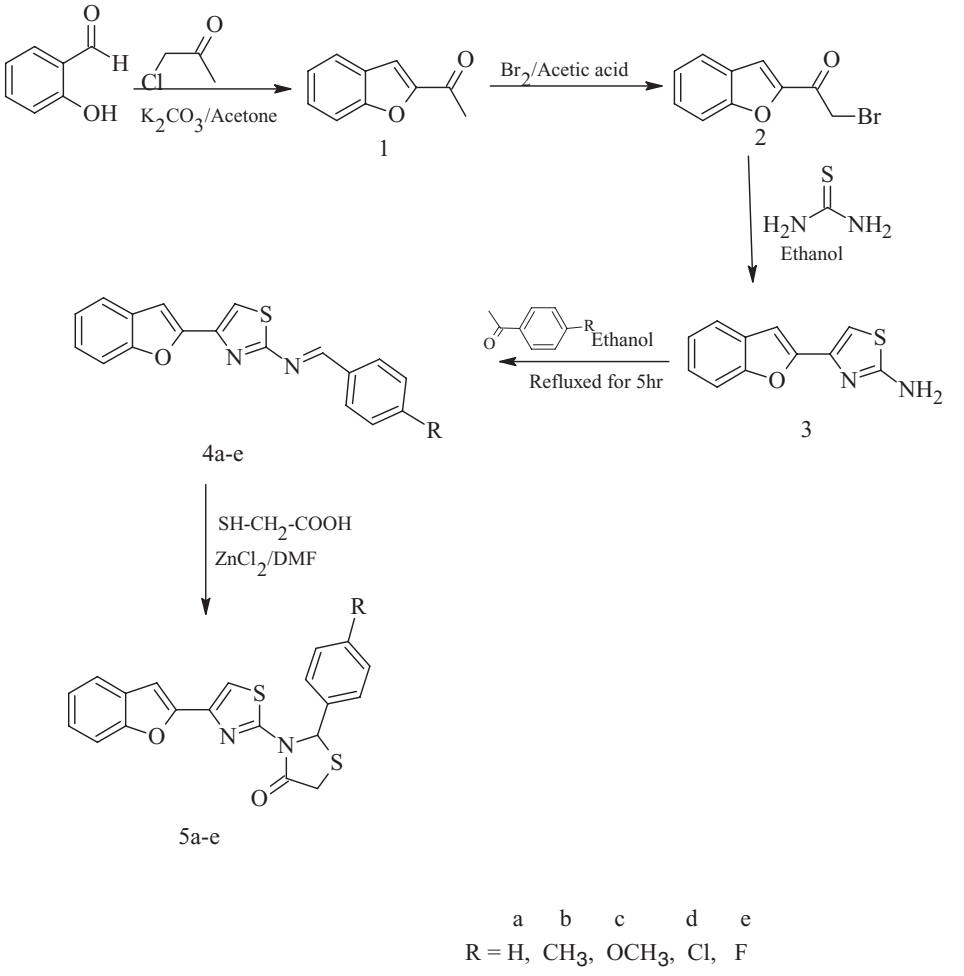

Scheme 1 Synthesis of thiazolidinone derivatives from different Schiff bases.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on Nicolet Impact 410 FT IR spectrophotometer using KBr pellets or Nujol. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300-MHz FT NMR spectrometer in $CDCl_3$ and DMSO-d_6 with TMS as internal standard. Chemical shifts are reported in parts per million (δ) and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; br, broad signal; and m, multiplet. Mass spectra were recorded on a Thermo-Finnigan-MATT, Bremen (Model MAT8200) spectrometer. Electrospray ionization mass spectrum (ESIMS) was recorded on a Quattro LCZ (Walters-Micromass, Manchester, UK) and elemental analyses were carried out using a Heraus CHN rapid analyzer. Thin layer chromatography (TLC) was performed on precoated sheets of silica gel 60 F_{254}.

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General Procedure for the Synthesis of 4-(1-Benzofuran-2-yl)-*N*-[(4-arylphenyl)methylidene]-1,3-thiazol-2-amine(4a–e)

An equimolar mixture of substituted arylaldehyde (0.001 mol) and 4-(1-benzofuran-2-yl)-1,3-thiazol-2-amine **3** (0.001mol) was taken in dry ethanol (5 mL) and refluxed for 5–6 h. The reaction mixture was cooled at room temperature and poured into ice water, filtered, and dried. The dried compounds (**5a–e**) were recrystallized in ethanol.

4-(1-Benzofuran-2-yl)-*N*-[phenylmethylidene]-1,3-thiazol-2-amine (4a). Colorless (ethanol), yield 82%, mp 176–178°C: IR (KBr) $\nu(cm^{-1})$: 3050, 1562, 1442 (C=C, C=N).^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.53 (s, 1H, CH) 6.89 (s, 1H, CH, thiazole), 7.36–8.07 (m, 10H, Ar-H), MS: m/z 304, Anal. $C_{18}H_{12}$ N_2OS calcd. for: C, 71.03; H, 3.97; N, 9.20. Found: C, 71.05; H, 3.97; N, 9.22%.

4-(1-Benzofuran-2-yl)-*N*-[(4-methylphenyl)methylidene]-1,3-thiazol-2-amine (4b). Brown (ethanol), yield 76%, mp 190–192°C: IR (KBr) $\nu(cm^{-1})$: 3061, 1538, 1464 (C=C, C=N).^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.25 (s, 3H), 2.58 (s, 1H, CH), 7.08 (s, 1H, CH, thiazole), 7.21–8.11(m, 9H, Ar-H), MS: m/z 318, Anal. $C_{19}H_{14}$ N_2OS calcd. for: C, 71.67; H, 4.43; N, 8.80. Found: C, 71.69; H, 4.44; N, 8.83%.

4-(1-Benzofuran-2-yl)-*N*-[(4-methoxyphenyl)methylidene]-1,3-thiazol-2-amine (4c). Colorless (ethanol), yield 61%, mp 188–190°C: IR (KBr) $\nu(cm^{-1})$: 3045, 1556, 1460 (C=C, C=N).^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.53 (s, 1H, CH), 3.62(s, 3H, OCH_3), 7.11 (s, 1H, CH, thiazole), 7.18–8.05(m, 9H, Ar-H), MS: m/z 334, Anal.$C_{19}H_{14}$ N_2O_2S calcd. for: C, 68.24; H, 4.22; N, 8.38. Found: C, 68.26; H, 4.24; N, 8.41%.

4-(1-Benzofuran-2-yl)-*N*-[(4-chlorophenyl)methylidene]-1,3-thiazol-2-amine (4d). Pale yellow (ethanol), yield 65%, mp 201–203°C: IR (KBr) $\nu(cm^{-1})$: 3055, 1550, 1463 (C=C, C=N).^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.48 (s, 1H, CH), 7.12 (s, 1H, CH, thiazole), 7.18–8.05 (m, 9H, Ar-H), MS: m/z 338, 339, Anal. $C_{18}H_{11}$ N_2OSCl calcd. for: C, 68.81; H, 3.27; N, 8.27. Found: C, 68.83; H, 3.30; N, 8.29%.

4-(1-Benzofuran-2-yl)-*N*-[(4-fluorophenyl)methylidene]-1,3-thiazol-2-amine (4e). Pale yellow (ethanol), yield 68%, mp 186–188°C: IR (KBr) $\nu(cm^{-1})$: 3064, 1548, 1436 (C=C, C=N).^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.50 (s, 1H, CH), 7.05 (s, 1H, CH, thiazole), 7.26–8.17 (m, 9H, Ar-H), MS: m/z 322, Anal. $C_{18}H_{11}$ N_2OSF calcd. for: C, 67.07; H, 3.44; N, 8.69. Found: C, 67.09; H, 3.45; N, 8.72%.

General Procedure for the Synthesis of 3-[4-(1-Benzofuran-2-yl)-1,3-thiazol-2-yl]-2-(4-aryl)-1,3-thiazolidin-4-one Derivatives (5a–e)

An equimolar mixture of (0.001 mol) Schiff bases (**4a–e**) and thioacetic acid (0.07 g, 0.001 mol) in catalytic amount of anhydrous $ZnCl_2$ were taken in DMF (5 mL) and refluxed for 6–8 h. Excess of DMF was distilled off, and the reaction mixture was poured into ice cold water, filtered, and dried to furnished 1,3-thiazolidin-4-one derivatives.

3-[4-(1-Benzofuran-2-yl)-1,3-thiazol-2-yl]-2-phenyl-1,3-thiazolidin-4-one (5a). Brown (ethanol), yield 56%, mp 184–186°C: IR (KBr) $\nu(cm^{-1})$: 3078, 2921–2856 (aromatic,Ar-H), 1669 (C=O), 1548, 1438 (C=C, C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.85 (s, 2H, methylene), 4.18 (s, 1H, methine), 7.21 (d, 1H, $J = 9.06$ Hz, 3-CH), 7.28 (s, 1H, CH, thiazole), 7.32 (dd, $J = 8.40$ Hz, 1H, 6-CH), 7.39 (dd, $J = 6.36$ Hz, 1H, 7-CH), 7.35 (d, $J = 3.65$ Hz, 2H, C_2, C_6H-Ph), 7.26 (d, $J = 3.42$ Hz, 2H,C_3, C_5H-Ph), 7.98 (d, 1H, $J = 8.16$ Hz, 8-CH), ^{13}C NMR (300 MHz, DMSO-d_6) δ_C (ppm): 33.5, 72.5,

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104.8, 120.3, 124.7, 126.3, 128.4, 129.8, 132.4, 134.6, 136.8, 140.5, 142.5, 149.8, 158.2, 171.2. MS: m/z 378, Anal. $C_{20}H_{14}N_2O_2S_2$ calcd. for: C,63.47; H,3.73; N, 7.40. Found: C, 63.45; H, 3.73; N, 7.42%.

3-[4-(1-Benzofuran-2-yl)-1,3-oxazol-2-yl]-2-(4-methylphenyl)-1,3-thiazolidin-4-one (5b). Yellow (ethanol), yield 65%, mp 159–162°C: IR (KBr) $\nu(cm^{-1})$: 3090, 2953–2824, 1674 (C=O), 1565, 1462 (C=C, C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.80 (s, 3H, CH3), 3.65 (s, 2H, methylene), 6.48 (s, 1H, methine), 7.32 (s, 1H, CH, thiazole), 7.26 (d, $J = 1.83$ Hz, 1H, 3-CH), 7.30 (dd, $J = 4.82$ Hz, 1H, 6-CH), 7.36 (d, $J = 4.41$ Hz, 2H,C_3, C_5H-Ph), 7.45 (dd, $J = 8.25$ Hz, 1H, 7-CH), 7.84 (d, $J = 5.61$ Hz, 1H, 8-CH), 7.98 (d, $J = 7.61$ Hz, 2H, C_2, C_6H-Ph), ^{13}C NMR (300 MHz, DMSO-d_6) δ_C (ppm): 21.6, 33.8, 71.9, 112.8, 122.9, 123.1, 126.3, 128.4, 130.4, 130.6, 133.5, 135.7, 140.0, 143.1, 149.2, 158.2,169.8, MS: m/z 392, Anal. $C_{21}H_{16}N_2O_2S_2$ calcd. for: C, 64.26; H, 4.11; N, 7.14. Found: C, 64.29; H, 4.12; N, 7.16%.

3-[4-(1-Benzofuran-2-yl)-1,3-oxazol-2-yl]-2-(4-chlorophenyl)-1,3-thiazolidin-4-one (5c). Colorless (ethanol), yield 82%, mp 241–243°C: IR (KBr) $\nu(cm^{-1})$: 3058, 2984–2852, 1672 (C=O), 1559, 1458 (C=C, C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.63 (s, 2H, methylene), 6.45 (s, 1H, methine), 7.18 (d, $J = 1.6$ Hz, 1H, 3-CH), 7.34 (s, 1H, CH, thiazole), 7.35 (dd, $J = 9.21$ Hz, 1H, 6-CH), 7.31 (d, $J = 7.77$ Hz, 2H,C_3, C_5H-Ph), 7.44 (dd, $J = 8.37$ Hz, 1H, 7-CH), 7.62 (d, $J = 7.52$ Hz, 1H, 8-CH), 7.96 (d, $J = 7.20$ Hz, 2H, C_2, C_6H-Ph), ^{13}C NMR (300 MHz, DMSO-d_6) δ_C (ppm): 33.2, 72.3, 115.8, 121.9, 123.4, 126.7, 128.5, 130.6, 132.4, 134.6, 135.4, 141.5, 143.3, 150.2, 154.6, 166.8. MS: m/z 412, Anal. $C_{20}H_{13}ClN_2O_2S_2$ calcd. for: C, 58.18; H, 3.17; N, 6.78. Found: C, 58.20; H, 3.16; N, 6.75%.

3-[4-(1-Benzofuran-2-yl)-1,3-oxazol-2-yl]-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one (5d). Yellow (ethanol), yield 68%, mp 211–213°C: IR (KBr) $\nu(cm^{-1})$: 3078, 2950–2838, 1672 (C=O), 1566, 1469 (C=C, C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 4.2 (s, 3H, OCH_3), 3.53 (s, 2H, methylene), 6.44 (s, 1H, methine), 7.28 (s, 1H, CH, thiazole), 7.18 (d, $J = 13.40$ Hz, 1H, 3-CH), 7.35 (dd, $J = 8.42$ Hz, 1H, 6-CH), 7.38 (dd, $J = 8.37$ Hz, 1H, 7-CH), 7.48 (d, $J = 8.57$ Hz, 2H, C_3, C_5H-Ph), 7.63 (d, $J = 7.76$ Hz, 1H, 8-CH), 7.68 (d, $J = 7.45$ Hz, 2H,C_2, C_6H-Ph), ^{13}C NMR (300 MHz, DMSO-d_6) δ_C (ppm): 65.0, 32.5, 70.7, 110.8, 123.8, 124.6, 125.2, 127.4, 130.6, 132.7, 134.1, 134.8, 141.3, 142.7, 149.8, 155.2, 171.8, MS: m/z 408, Anal. $C_{21}H_{16}N_2O_3S_2$ calcd. for: C, 61.75; H, 3.95; N, 6.86. Found: C, 61.78; H, 3.98; N, 6.83%.

3-[4-(1-Benzofuran-2-yl)-1,3-oxazol-2-yl]-2-(4-fluorophenyl)-1,3-thiazolidin-4-one (5e). Yellow (ethanol), yield 65%, mp 204–206°C: IR (KBr) $\nu(cm^{-1})$: 3051, 2946–2867, 1668 (C=O), 1559, 1463 (C=C, C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.64 (s, 2H, methylene), 6.62 (s, 1H, methine), 7.10 (d, $J = 7.62$ Hz, 1H, 3-CH), 7.36 (dd, $J = 8.10$ Hz, 1H, 6-CH), 7.37 (s, 1H, CH, thiazole), 7.49 (dd, $J = 7.64$ Hz, 1H, 7-CH), 7.31 (d, $J = 7.35$ Hz, 2H, C_2, C_6H-Ph), 7.73 (d, $J = 8.46$ Hz, 1H, 8-CH), 7.84 (d, $J = 7.78$ Hz, 2H, C_3, C_5H-Ph), ^{13}C NMR (300 MHz, DMSO-d_6) δ_C (ppm): 33.0, 72.5, 112.3, 120.6, 122.7, 125.8, 128.8, 131.0, 134.1, 135.9, 135.5, 140.8, 144.5, 148.8, 154.2, 170.8. MS: m/z 396, Anal. $C_{20}H_{13}N_2O_2S_2$ calcd. for: C, 60.59; H, 3.31; N, 7.07. Found: C, 60.55; H, 3.34; N, 7.08%.

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