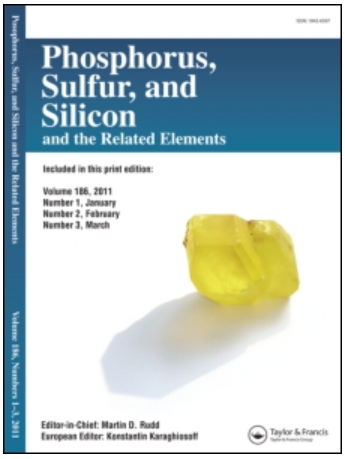

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A Facile Synthesis of Bromo-Substituted Benzofuran Containing Thiazolidinone Nucleus Bridged with Quinoline Derivatives: Potent Analgesic and Antimicrobial Agents

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A FACILE SYNTHESIS OF BROMO-SUBSTITUTED BENZOFURAN CONTAINING THIAZOLIDINONE NUCLEUS BRIDGED WITH QUINOLINE DERIVATIVES: POTENT ANALGESIC AND ANTIMICROBIAL AGENTS

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Treatment of 5-bromo-2-acetyl benzofuran with hydrazine followed by condensation of the resulting hydrazone with different quinoline derivatives gave the corresponding Schiff bases. Reaction of these Schiff bases with thioacetic acid furnished the target thiazolidinone molecule. Some of the newly synthesized compounds show promising analgesic and antimicrobial activity.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Antimicrobial agent; 5-bromo-salicylaldehyde; cyclic voltammetry; quinoline derivatives; Schiff base; thioacetic acid

INTRODUCTION

Benzo[*b*]furans are of great synthetic interest because of their wide distribution in nature and useful biological activities.[1] The benzo[*b*]furan ring is often incorporated in pharmaceutical agents as a core structural motif, and as a result it continues to attract extensive synthetic efforts.[2,3] Many reported synthetic approaches are based on the construction of furan rings from various arene derivatives.[3h] Benzofuran and its derivatives exhibit various biological activities. Such derivatives were investigated as antibacterial[4] or antifungal agents.[4,5] Moreover, many researchers have synthesized fused or coupled nitrogen-containing heterocycles,[6,7] which have shown very good biological activities. Quinoline is the important nitrogen-containing heterocyclic compound having biological activity. The presence of a halogen atom also shows good antimicrobial properties.[8] Quinoline and its derivatives are known for their antimalarial and therapeutic effects.[9] A number of quinoline

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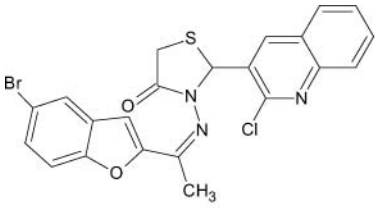
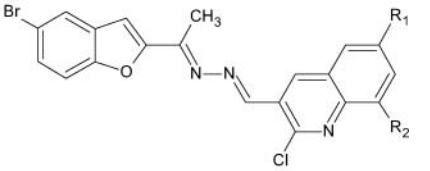
derivatives are known to possess antibacterial, antifungal, antihypertensive, analgesic, and anti-inflammatory activities.[10–13] The applications of quinoline derivatives[14–17] are impressive, spreading from antimalarial to almost every branch of medicinal chemistry.[18,19]

In continuation of work on condensed heterocycles[20–22] and in view of our growing interest in the field of bioactive agents, in this article we report an efficient synthesis of novel compounds **5a–e** and **6a** for their profile of analgesic and antimicrobial activities.



6a

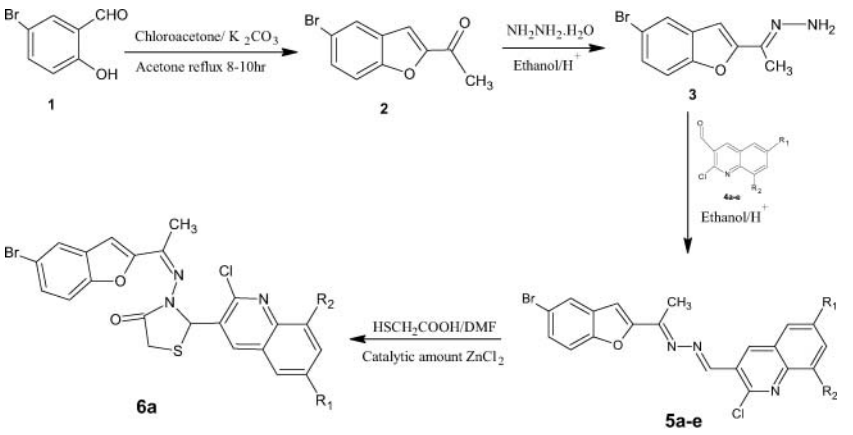


5a-e

RESULTS AND DISCUSSION

In continuation of our studies in developing condensed quinoline derivatives due to their significant biological activities, it appeared expedient to synthesize a series of systematically condensed and appropriately functionalized 3-{[1-(5-bromo-1*H*-inden-2-yl)ethylidene]amino}-2-(2-chloroquinolin-3-yl)-1,3-thiazolidin-4-ones **6a**. The starting material, 5-bromo-2-acetyl benzofuran **2** was prepared by the reaction of 5-bromo-2-hydroxy benzaldehyde with chloroacetone in anhydrous acetone.[23,24] Compound **2** was reacted with hydrazine hydrate under acidic conditions in ethanol at reflux temperature to form 1-(5-bromo-1-benzofuran-2-yl)ethanone hydrazone **3** in good yield. The structure of **3** was confirmed by IR and ^{1}H NMR data. The IR spectrum of **3** showed a sharp absorption band at 3300–3400 cm^{-1} due to NH_2 group. The absence of a carbonyl stretching frequency at 1665 cm^{-1} and the appearance of an absorption band at 3300–3400 cm^{-1} reveals the formation of hydrazone **3**. The ^{1}H NMR spectrum of compound **3** exhibits a broad singlet at δ 5.63 ppm for $–NH_2$ protons, another singlet at δ 1.63 ppm due to three methyl protons, and a multiplet between δ 7.22–7.78 ppm for aromatic protons.

The treatment of compound **3** with different substituted 2-chloro-3-formyl quinolines[25] **4a–e** in the presence of a catalytic amount of acetic acid in absolute ethanol furnished the Schiff bases **5a–e** (Scheme 1. The structures of the newly synthesized Schiff bases were confirmed by IR, ^{1}H NMR, and mass spectral data. The IR spectrum of **5a** exhibits absorption bands at 1615 and 1618 cm^{-1} due to two $-C{=}N$ groups. ^{1}H NMR spectrum of **5a** displayed a multiplet between δ 7.27–7.86 ppm for nine aromatic protons and a sharp intensive singlet at δ 1.64 ppm due to $–CH_3$ protons. The absence of a singlet at δ 5.58 ppm due to $–NH_2$ protons revealed the formation of desired compounds **5a**, and it also showed the isotopic peaks at m/z 427 and 429. The structure was further confirmed from its mass spectrum, which gave the molecular ion peak at m/z 425 (M^+) that corresponds to molecular weight of compound **5a**. Similarly, the structures of the compounds **5b–e** were assigned on the basis of their spectral data. Cyclization of Schiff base **5a** with thioacetic acid in DMF at reflux temperature using a catalytic amount of anhydrous $ZnCl_2$ furnished the compound, which was identified as 3-{[1-(5-bromo-1-benzofuran-2-yl)ethylidene]amino}-2-(2-chloroquinolin-3-yl)-1,3-thiazolidin-4-one (**6a**) on the basis of



Compound	R_1	R_2
A	H	H
B	CH_3	H
C	H	CH_3
D	H	OCH_3
E	OCH_3	H

Scheme 1

spectral data. The IR spectrum of **6a** exhibits absorption bands at 1676 cm^{-1} due to a carbonyl stretching and 1620 cm^{-1} due to a C=N. Its mass spectrum showed a molecular ion peak(M^+) at m/z 500 and isotopic peaks at m/z 502 and 504 in the intensity ratio of 3:4:1. The ^1H NMR spectrum of compound **6a** displayed four signals—a singlet at δ 1.06 ppm due to three methyl protons, another two singlets at δ 3.12 ppm (2H) and δ 4.56 ppm (1H) due to methylene and methine protons of thiazolidone ring, respectively, and nine aromatic protons appeared as a multiplet between δ 7.14–8.28 ppm.

BIOLOGICAL STUDIES

Antimicrobial Activity

The newly synthesized compounds were screened for their antimicrobial activity by the cup plate method.[26] The in vitro anitimicrobial activity was carried out against 24 h old cultures of four bacteria and four fungal organisms. (See the Supplemental Materials online.)

Cyclic Voltammetric Studies of Compound 5a

Figure 1 shows the cyclic voltammogram of chloroquinoline-3-carbaldehyde[1-(5-bromo-1-benzofuran-2-yl)ethylidene] hydrazone at a glassy carbon electrode in 20 mM

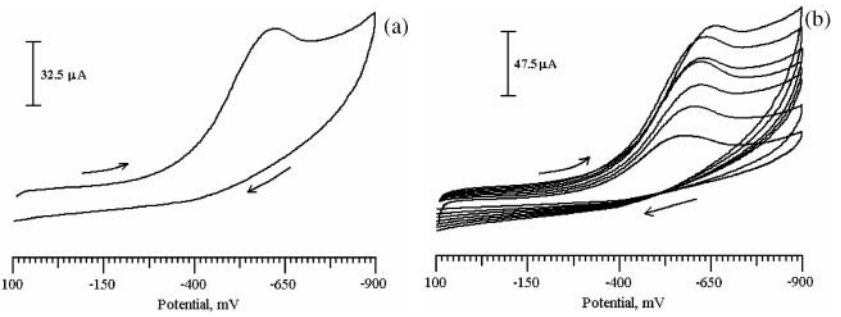
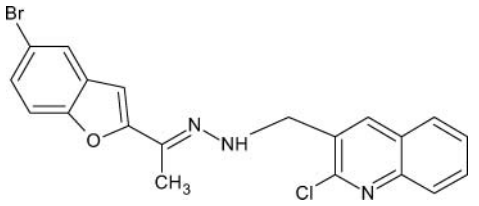


Figure 1 (a) The cyclic voltammogram of 1 mM comp **5a** in 20 mM sulfuric acid media at glassy carbon electrode. (b) Variation of scan rate from 20 mVs^{-1} to 140 mVs^{-1}.

sulfuric acid media at 50 mV s^{-1}. The compound showed a cathodic peak potential at –618 mV for the reduction of the −C=N moiety. The irreversibility was confirmed by the absence of an anodic peak between the potential of +100 mV to –900 mV. The effect of the scan rate was studied from 20 to 250 mVs^{-1}, and the cathodic peak current was proportional to the scan rate and the process is diffusion-controlled. The calculated number of electrons was found to be 1.96, which is close to the two-electron change during the electrochemical reaction. From the graph, we can see that the −C=N− group in the Schiff base is easily reduced at the glassy carbon electrode by cyclic voltammetry. From this evidence, the probable structure for reduced compound may be as shown in Scheme 2.



Scheme 2 The probable structure for reduced compound **5a**.

EXPERIMENTAL

The melting points were determined in an open capillary tube and are uncorrected. The purity of the compounds was checked by TLC on silica gel and was purified by column chromatography. ^{1}H NMR spectra (300 MHz) were recorded on a Bruker Supercon FT NMR instrument using TMS as an internal standard, and chemical shifts are expressed in δ units. IR spectra were recorded on a Perkin Elmer 157 Infrared Spectrophotometer and mass spectra on a Jeol JMS-D 300 mass spectrometer operating at 70 eV.

General Procedure

Synthesis of aryl hydrazone (3a). The mixture of 1-(5-bromo-1-benzofuran-2-yl)ethanone **(2)** (10 mmol, 0.8g) and hydrazine hydrate (98%, 0.01 mol) was refluxed in ethanol for 6 h. The excess ethanol was distilled out, and the contents were allowed to cool.

The crystals formed were filtered and dried. The completion of the reaction was monitored on TLC by using silica gel-G coated plates by using ethyl acetate and pet ether (1:1) as the eluent and observed under UV light. IR (KBr) (cm^{-1}): 3300–3400 (NH_2), 3056 (aromatic −CH stretching), 1586, 1573 (C=C ring stretching), 2970, 2848 (methyl CH stretching), 1284 (N-N=C). ^{1}H NMR (300 MHz) (DMSO-*d*6) (δ) ppm; 1.63 (s, 3H, CH_3); 5.63 (s, 2H, NH_2); 7.22–7.78 (4H, aromatic).

Chloroquinoline-3-carbaldehyde-[1-(5-bromo-1-benzofuran-2-yl)ethylidene] Hydrazone (5a). A mixture of 1-(5-bromo-1-benzofuran-2-yl) ethanone hydrazone **3** (0.25 g, 0.001mol) and 2-chloroquinoline-3-carbaldehyde **4a** (0.19g, 0.01mole) was taken in ethanol (10 mL) with a catalytic amount of acetic acid and heated at reflux temperature for 5–6 h. After the completion of the reaction (checked by TLC), the reaction mixture was poured onto crushed ice. The solid mass thus separated out was filtered, washed with water, and crystallized from ethanol to give the desired compound **5a** in 83% yield, mp 216–218 °C; IR (KBr, cm^{-1}) 1618, and 3058(aromatic ring); Calc.: $C_{20}H_{13}BrClN_3O$: C, 56.30; H, 3.07; N, 9.85; Anal. Found: C, 56.44; H, 3.32; N, 10.15; MS: m/z 425; ^{1}H NMR: (DMSO-d_6): δ 1.64 (s, 3H), δ 7.20 (1H, CH), δ 7.27–7.86 (m, 9H, Ar−H).

3-[[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]hydrazinylidenemethyl-2-chloro-6-methylquinoline (5b). The same procedure was followed as for **5a.** Yellow solid, crystallized from ethanol, 75% yield, mp 223–226 °C; IR (KBr, cm^{-1}), Aromatic C−H stretching 3070, 3030, Methyl (C−H)2869, (C=N) 1689; Calc.: $C_{21}H_{15}BrClN_3O$: C, 57.23; H, 3.43; N, 9.53; Anal. Found: C, 57.39; H, 3.47; N, 9.91; MS: m/z 439; ^{1}H NMR: (DMSO-d_6): δ 1.78(s, 3H), δ 2.15(s, 3H), δ 7.18 (1H, CH), δ 7.34–8.86 (m, 8H, Ar−H).

3-[[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]hydrazinylidenemethyl]-2-chloro-8-methylquinoline (5c). The same procedure was followed as for **5a**. Yellow solid, crystallized from ethanol, 60% yield, mp 206–209 °C; IR (KBr, cm^{-1}), Aromatic C−H stretching 3070,3030, Methyl (C−H) 2893, (C=N) 1689; Anal. Calc.: $C_{21}H_{15}BrClN_3O$: C, 57.23; H, 3.43; N, 9.53; Anal. Found: C, 57.41; H, 3.51; N, 9.58 MS: m/z 439; ^{1}H NMR: (DMSO-d_6): δ 1.65 (s, 3H), δ 2.35 (s, 3H), δ 7.18(1H, CH), δ 7.34–8.86 (m, 8H, Ar−H).

3-[[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]hydrazinylidenemethyl]-2-chloro-6-methoxyquinoline (5d). The same procedure was followed as for **5a**. Pale yellow solid, Crystallized from ethanol, 65% yield, mp 236–238 °C; IR (KBr, cm^{-1}), Aromatic C−H stretching 3070, 3030, Methyl (C−H) 2893, (C=N) 1689; Calc.: $C_{21}H_{15}BrClN_3O_2$: C, 55.23; H, 3.31; N, 9.20; Anal. Found: C, 55.39; H, 3.42; N, 9.45; MS: m/z 455; ^{1}H NMR: (DMSO-d_6): δ 1.45 (s, 3H), δ 3.44 (s, 3H), δ 7.20(1H, CH), δ 7.14–8.36 (m, 8H, Ar−H).

3-[[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]hydrazinylidenemethyl]-2-chloro-8-methoxyquinoline (5e). The same procedure was followed as for **5a**. Greenish yellow solid, crystallized from ethanol, 77% yield, mp 209–212 °C; IR (KBr, cm^{-1}), Aromatic C−H stretching 3070,3030, Methyl (C−H) 2893, (C=N) 1689; $C_{21}H_{15}BrClN_3O_2$: Calc.: C, 55.23; H, 3.31; N, 9.20; Anal. Found: C, 55.41; H, 3.39; N, 9.82; MS: m/z, 455; ^{1}H NMR: (DMSO-d_6): δ 1.25 (s,3H), δ 3.94 (s,3H), δ 7.08 (1H,CH), δ 7.14–7.96 (m, 8H, Ar−H).

3-{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino}-2-(2-chloroquinolin-3-yl)-1,3-thiazolidin-4-one (6a). 3-[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]hydrazinylidene}methyl]-2-chloroquinoline (0.001 mol, 0.426 g) and mercaptoacetic acid

(0.01 mol, 1.84 g) were refluxed in the presence of a catalytic amount of anhydrous $ZnCl_2$ in dry DMF (25 mL) for 6 h. The reaction mixture was then cooled and poured onto crushed ice. The product that separated out was filtered, dried, and recrystallized from ethanol as a light brown solid. Yield 86%, mp 239–241°C; IR (KBr, cm^{-1}), carbonyl (C═O) 1676, Aromatic C—H stretching 3070, 3030, Methyl (C—H) 2893, (C═N) 1620; Calc.: $C_{22}H_{15}BrClN_3O_2S$; C, 52.76; H, 3.02; N, 8.39; Anal. Found: C, 52.93; H, 3.28; N, 8.45; MS: m/z 500; ^{1}H NMR (DMSO-d_6): δ 1.06(s,3H), δ 3.12 (m, 2H), δ 4.56 (1H), δ 7.14–8.28 (m, 9H, Ar—H).

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