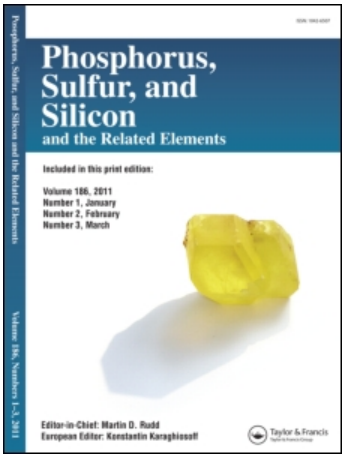

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An Efficient, Microwave-Assisted, One-Pot Synthesis of Dioxolano Quinoline/benzo[*h*]quinolines as Potent Antibacterial Agents

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AN EFFICIENT, MICROWAVE-ASSISTED, ONE-POT SYNTHESIS OF DIOXOLANO QUINOLINE/BENZO[*h*]QUINOLINES AS POTENT ANTIBACTERIAL AGENTS

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Quinolines/benzo[*h*]quinolines are associated with a broad spectrum of biological activities. In view of this, 3-(1,3-dioxolan-2-yl)quinoline/benzo[*h*]quinoline-2-thiol/selenols were prepared under microwave irradiation through one-pot reactions, and these quinolines/benzo[*h*]quinolines were evaluated for potential antibacterial 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 Antibacterial agents; microwave; quinolines/benzo[*h*]quinolines

INTRODUCTION

The quinoline nucleus occurs in several natural compounds (cincona alkaloids) and pharmacologically active substances that display a broad range of biological activity.[1] The biological activity of quinoline compounds has been found in the form of antiasthmatic,[2] antibacterial,[3] antiinflammatory,[4] and antihypertensive[5] properties. In addition to medicinal applications, quinolines have been employed in the study of bioorganic and bioorganometallic processes.[6]

Numerous planar nitrogen heterocycles, such as amsacrine, the benzo[*c*]phenan thridines, the ellipticines, intoplicine, and coralyne are well known as topoisomerase inhibitors and have been investigated as potential anticancer agents.[7–11] The benzo[*h*] quinolines can be viewed as being structurally related to the antitumor benzo[*c*] phenanthridines by deletion of a ring, or as heterocyclic isomers of the abovementioned acridine- and phenanthridine-based antitumor agents. Consequently, given routes to

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2-chlorobenzo[*h*]quinoline-3-carbaldehyde, and to the 4-chloro-isomer, a range of benzo[*h*]quinolines of potential biological interest will become available.

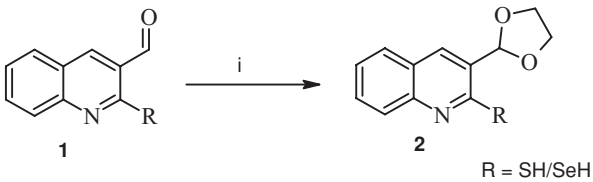
Recent studies reveal that the intramolecularly stabilized organoselenium and sulfur compounds play an important role in catalytic antioxidant activity.[12] Since selenium (Se) resembles sulfur (S) in many of its properties, it is isosteric.[13,14] The biological and pharmaceutical activities of different selenium compounds are of special interest, because it is an active site of a large number of selenium-dependent enzymes, such as glutathione peroxidase (GSHPx)[15,16] and prevention of cancer.[17] In the same field of research, the results of many studies[18,19] have related Se-deficient bioavailability and intake to human cancer mortality. New synthetic selenium compounds may provide a way to minimize toxicity associated with higher selenium intake. Recently, several forms of organoselenium have been studied for their cancer preventive activities. The dietary *p*-methoxybenzeneselenol, a synthetic organoselenium compound, was found to inhibit azoxymethane-induced hepatocarcinogenesis in rats without clinical signs of toxicity.[20]

Due to the great pharmacological importance of quinolines/benzo[h]quinolines, and with the above facts, we carried out the synthesis of some new heterocycles such as sulfur- and selenium-containing fused quinoline in order to enhance the biological activity.

RESULTS AND DISCUSSION

Chemistry

Generally, planar fused quinolines/benzo[h]quinolines containing two or more hetero atoms are found to have valuable pharmacological activities as mentioned earlier, and therefore, they are useful compounds in medicinal research. Hence, in continuation of our research work on developing new quinoline containing heterocycles due to their significant biological activities, it appeared expedient to synthesize a series of condensed and appropriately funtionalized sulfur- and selenium-containing 1,3-dioxolan-quinoline/benzo[*h*]quinolines. The starting compounds 2-mercapto/seleno-3-formyl quinolines/benzo[h]quinoline (**1a**, **1b** and **3a**, **3b**) were prepared according to the method in the literature.[21] The 3-(1,3-dioxolan-2-yl)quinoline/benzo[h]quinoline -2-thiol/selenols (**2a**, **2b** and **4a**, **4b**) were obtained in one pot by the cyclization of 2-mercapto/seleno-3-formylquinolines/benzo[*h*]quinolines in the presence of *p*-TsOH catalyst and ethylene glycol under microwave irradiation in good yields. This method provided good yield of products in 5–6 min (Table I), making it a useful method for the synthesis of condensed quinolines.



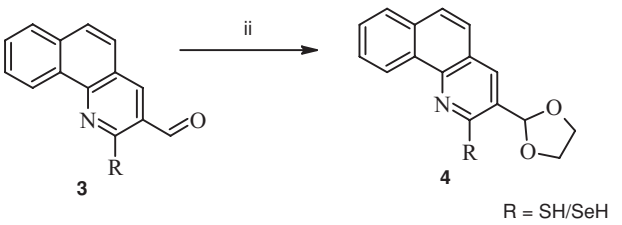
(i) ethylene glycol, toluene-*p*-sulfonic acid, toluene, MW-irradiation, 5–6 min

Scheme 1 Reaction pathway for the synthesis of desired compounds.

Table I Reaction time data of both conventional and MW methods

Compound	Time (h) Conventional heating	Time (min) MW
2a	3.0–.0	5.0–6.0
2b	4.0–5.0	5.5–7.0
4a	4.5–5.0	5.0–6.0
4b	5.0–6.0	6.0–7.0

The structure of the compounds was confirmed on the basis of elemental analysis and spectral data (see the Experimental section). As an example, the IR (KBr) spectrum of compound **2a** showed an absence of −CHO stretching frequency at around 1670 cm^{-1}, which appeared in the 2-mercapto/seleno-3-formylquinoline/benzo[h]quinolines. The ^1H NMR (DMSO-d_6) spectrum, in addition to aromatic protons resonated between δ 7.0–8.00 ppm (5–7H), exhibited a multiplet at δ 4.1–4.6 ppm corresponding to $-CH_2 \times 2$ protons, and a broad singlet at δ 10.1–10.9 ppm for –SH/SeH proton indicated the attachment of the reactive partner to the quinoline substrate. Finally, the structures were confirmed by their mass spectrum through the appearance of a molecular ion peak at m/z (M+) for all the synthesized compounds, as presented in the Experimental section. The obtained elemental analysis values are in agreement with theoretical data. We synthesized four more title compounds, which exhibited similar spectral characteristics (Schemes 1 and 2).



(ii) ethylene glycol, toluene-*p*-sulfonic acid, toluene, MW-irradiation, 5–6 mins

Scheme 2 Reaction pathway for the synthesis of desired compounds.

Antibacterial Activity

The results of antibacterial activity between synthesized compounds **2a**, **2b** and **4a**, **4b** and ciprofloxacin showed a synchronizing effect on strains of pathogenic bacteria. (See Table II, available online in the Supplemental Materials.)

EXPERIMENTAL

Chemistry

The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates using petroleum ether:ethyl acetate solvent (v:v 1:1). Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded in KBr pellets on a Perkin-Elmer 157 IR spectrophotometer. ^1H NMR spectra were recorded in

DMSO-d_6 on an EM-390 (300 MHz) NMR spectrometer, and mass spectra were recorded on a MASPEC low resolution instrument operating at 70 eV.

Genral Procedure for the Synthesis of 3-(1,3-Dioxolan-2-yl)quinoline/ benzo[h]quinoline-2-thiol/selenol

A dry, 50-mL flask was charged with 2-mercapto/seleno-3-formyl quinolines/ benzo[*h*]quinoline (8 mmol) in toluene (100 mL) containing ethylene glycol (24 mmol) and a trace amount of toluene-*p*-sulfonic acid. The mixture was well mixed and then irradiated in a SANYOEM-350S microwave oven at 300 W for a designated time as required for completing the reaction (determined by TLC), as shown in Table I. Then, after being cooled to room temperature, the reaction mass was poured onto crushed ice, solid material was filtered off, and the crude product was purified by recrystallization from DMF. A similar reaction procedure has been followed for other derivatives.

3-(1,3-Dioxolan-2-yl)quinoline-2-thiol (2a). Pale yellow solid, Yield 71%, mp 255–257°C; IR (ν) (KBr) cm^{-1}; 3025 (C—H, Ar—H); 2590 (S—H); ^{1}H NMR (DMSO d_6), δ 7.15–7.95 (m, 5H, Ar—H), 6.34 (s, 1H, CH), 10.72 (s, 1H, SH), 4.15–4.35 (m, 4H, $CH_2 \times 2$); m/z (%) [M]+: [233]+; Elemental anlysis, Found: C, 61.79; H, 4.71; N, 5.91. Calculated for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00.

3-(1,3-Dioxolan-2-yl)quinoline-2-selenol (2b). Dark yellow solid, Yield 63%, mp 271–273°C; IR (ν) (KBr) cm^{-1}; 3035 (C—H, Ar—H); 2685 (Se—H); ^{1}H NMR (DMSO d_6), ^{1}H NMR (DMSO d_6), δ 7.26–7.89 (m, 5H, Ar—H), 6.52 (s, 1H, CH), 10.54 (s, 1H, SeH), 4.10–4.37 (m, 4H, $CH_2 \times 2$); m/z (%) [M]+: [280]+; Elemental anlysis, Found: C, 51.38; H, 3.91; N, 5.08. Calculated for $C_{15}H_{11}NO_2Se$: C, 51.44; H, 3.96; N, 5.00.

3-(1,3-Dioxolan-2-yl)benzo[h]quinoline-2-thiol (4a). Brown solid, Yield 69%, mp 268–270°C; IR (ν) (KBr) cm^{-1}; 3019 (C—H, Ar—H); 2596 (S—H); ^{1}H NMR (DMSO d_6), δ 7.15–7.85 (m, 7H, Ar—H), 6.44 (s, 1H, CH), 10.76 (s, 1H, SH), 4.15–4.35 (m, 4H, $CH_2 \times 2$); m/z (%) [M]+: [283]+; Elemental anlysis, Found: C, 67.75; H, 4.58; N, 4.86. Calculated for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.62; N, 4.94.

3-(1,3-Dioxolan-2-yl) benzo[h]quinoline-2-selenol (4b). Dark brown solid, Yield 60%, mp 279–281°C; IR (ν) (KBr) cm^{-1}; 3044 (C—H, Ar—H); 2698 (Se—H); ^{1}H NMR (DMSO d_6), δ 7.26–7.98 (m, 7H, Ar—H), 6.62 (s, 1H, CH), 10.64 (s, 1H, SeH), 4.26–4.38 (m, 4H, $CH_2 \times 2$); m/z (%) [M]+: [330]+; Elemental anlysis, Found: C, 58.26; H, 3.91; N, 4.18. Calculated for $C_{15}H_{11}N$: C, 58.19; H, 3.97; N, 4.24.

Antibacterial Assay

The agar well diffusion method[25] was used for the assessment of antibacterial activity of the test samples. (See the Supplemental Materials online.)

Bacterial Strains

Six clinical strains of three of the Gram-positive bacterial pathogens (*Staphylococcus aureus*—ATCC-29737, *Bacillus subtilis*—NCIM-2010, and *Staphylococcus pyognes*—NCIM-2608) and Gram-negative bacteria (*Pseudomonas aeruginosa*—ATCC-20852, *Klebsiella pneumoniae*—MTCC-618, and *Escherichia coli*) were collected from National Chemical Laboratory (NCL), Pune, India. (See the Supplemental Materials online.)

Statistical Analysis

The results of these experiments are expressed as mean ± SE of three replicates in each test. The data were evaluated by one-way analysis of variance (ANOVA), and mean separations were carried out using Duncan's multiple range test[26] to assess the statistical significance. $P \leq 0.05$ was considered as statistically significant, using statistical software SPSS ver. 11 (SPSS Inc., Chicago, USA).

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