Chapter

Introductory Chapter: Synthesis and Antimicrobial Activities of Dihydroazeto[2′,3′:4,5]seleno[2,3-*b*]quinolines

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1. Introduction

Literature survey reveals that sulfur- and selenium-containing molecules have attracted great importance in synthetic organic chemistry; particularly, aromatic five- and six-membered heterocycles fused or bridged to quinoline ring in linear fashion are found in many natural products due to their great pharmacological importance [1–7].

Substituted 2-azetidinone is an important class of compound for its importance in β-lactam antibiotic synthesis [8–10]. β-Lactam drugs in heterocycles are still the most widely prescribed antibiotics used in medicine [11]. The discovery of penicillin 2-azetidinone-based heterocycles have been one of the main classes of drugs with wide therapeutic activities, viz. anticonvulsant [12], anti-inflammatory [13], antibacterial [14], herbicidal [15], and also functioning as enzyme inhibitor [16] and are effective on central nervous system.

The conversion of aryl quinolines into dihydroazeto[2′,3′:4,5]seleno[2,3-*b*]quinolines is of vital importance in synthetic organic chemistry. Seleno[2,3-*b*]quinolines are prepared via their corresponding halogenated derivatives. In the current approach, we have planned to synthesize title compounds by efficient methods for the synthesis of seleno[2,3-*b*]quinolines, starting from easily accessible dichloro substituents by a reaction with sodium hydrogen selenide in water media with quantitative yield under remarkably soft conditions. Also, we came to know that good results were achieved using sodium hydrogen selenide (NaHSe). Here, we wish to examine the feasibility and efficiency of an approach to synthesis of some new seleno[2,3-*b*]quinolines.

In continuation of our research program directed toward the studies on Sulfur Chemistry [17–30] and synthesis of new potentially bioactive molecules, we were in need of a medicinal, bioorganic, industrial, cost-effective and commercial method for the synthesis of quinoline-based sulfur and selenium compounds. Also, the extensive biological properties and pharmaceutical applications have attracted interests in development of such sulfur and selenium-containing analogs.

2. Results and discussions

In this contribution, we focused our attention on the fast and efficient synthesis of dihydroazeto[2′,3′:4,5]seleno[2,3-*b*]quinolines. At first, the key intermediate 3-formyl-2-chloroquinoline [31] and azitidones [32] have been prepared from available reported methods.

In the current investigation very interesting result was observed in the reaction of **1a–e** on subjected to ring cyclisation with sodium hydrogen selenide in water offered seleno quinolines **2a**–**e**. As expected, the ^{1}H NMR spectrum exhibited two peaks at δ 5.71 ppm and δ 4.91 ppm of two protons present in azetidinone ring, i.e., -N-CH-C- and -Se-CH- of newly formed thieno ring. The aromatic protons resonate as multiplets at δ 7.26–8.50 ppm. The structure was further confirmed by recording its mass spectra. It gave the molecular ion peak at m/z 351(M^+) which corresponds to molecular formula $C_{18}H_{12}N_2OSe$. Also, halogen test was used to confirm the absence of chlorine.

3. Experimental

IR spectra were taken on a Perkin Elmer 157 Infrared spectrophotometer. ^{1}H NMR spectra (300 MHz) were recorded on a Bruker supercon FT-NMR instrument using TMS as internal standard and mass spectra on a Jeol JMS-D 300 mass spectrometer operating at 70 eV. Melting points were determined in open capillary and are uncorrected. Purity of the compounds was checked by TLC on silica gel and the compounds were purified by column chromatography.

3.1 Preparation of sodium hydrogen selenide

A mixture of 1 g of selenium powder and 25 ml of water was taken in a 500 ml beaker. The heat obtained was controlled by keeping this mixture at ice cold condition. A calculated amount of sodium borohydride of 0.026 moles was added in stepwise with constant stirring. During this, immediate liberation of foaming takes place because of the formation of hydrogen gas. Once the addition of sodium borohydride is over, approximately 25 ml of water was added along the side of the beaker and stirring was continued over 15 min. During this, a colorless, deep, reddish NaHSe formed and thus the obtained result was used without further any purification.

3.2 Preparation of dihydroazeto[2′,3′:4,5]seleno[2,3-*b*]quinolines (2a: E)

About 0.01 mole of azitidone **1a**, and 0.01 mole sodium hydrogen selenide, and 50 ml of water were taken in a 500-ml round-bottom flask. The contents of the flask were refluxed over 10–15 min on a water bath. The crystalline solid **2a** was precipitated in the flask. The contents of the flask was poured into a beaker containing 500 mL ice cold water, stirred, filtered, and finally, washed with ethanol. The compound obtained was dried, and recrystallized from ethyl acetate. In the same way the compounds, **2b–e** were prepared (**Figure 1**).

2a. 1-Phenyl-2a, 7b-dihydroazeto[2′,3′:4,5]seleno[2,3-*b*]quinoline

Solid, mp. 280°C; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (ppm): 4.91 (1H, s, -Se-CH-), 5.71 (1H, s, -N-CH-C), 7.26–8.50 (10H, m, Ar-H); IR (KBr) ν (cm^{-1}): 1735.81 (C=O azetidinone), 1653. [M+], 351. Calcd. (%) for $C_{18}H_{12}N_2OSe$: C; 61.55, H; 3.44, N; 7.98, Se; 22.48, Found: C; 61.08, H; 3.44, N; 7.95, Se; 22.43.

2b. 1-(4-Methylphenyl)-2a,7b-dihydroazeto[2′,3′:4,5]seleno[2,3-*b*]quinoline

Solid, mp. 272°C; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (ppm): 2.60 (s, -CH_3), 4.87 (1H, s, -Se-CH-), 5.89 (1H, s, -N-CH-C), 7.20–8.49 (9H, m, Ar-H); IR (KBr) ν (cm^{-1}): 1735.61 (C=O azetidinone), [M+], 365. Calcd. (%) for $C_{19}H_{14}N_2OSe$: C; 62.47, H; 3.86, N; 7.67, Se; 21.62, Found: C; 62.45, H; 3.83, N; 7.64, Se; 21.65.

2c. 1-(4-Methoxyphenyl)-2a,7b-dihydroazeto[2′,3′:4,5]seleno[2,3-*b*]quinoline

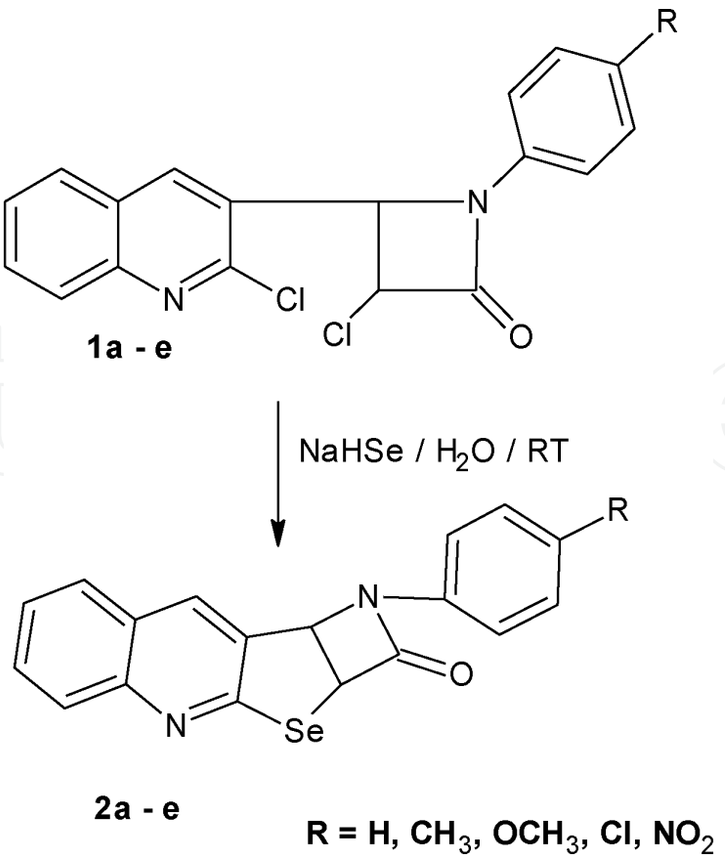

Figure 1.
*General synthetic procedure for dihydroazeto[2′,3′:4,5]seleno[2,3-*b*]quinolines.*

Solid, mp. 287°C; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (ppm): 3.90 (s, -OCH_3), 4.92 (1H, s, -Se-CH-), 5.79 (1H, s, -N-CH-C), 7.23–8.42 (9H, m, Ar-H); [M+], 381. Calcd. (%) for $C_{19}H_{14}N_2O_2Se$: C; 59.85, H; 3.70, N; 7.35, Se; 20.71. Found: C; 59.87, H; 3.73, N; 7.39, Se; 20.73.

2d. 1-(4-Chlorophenyl)-2a,7b-dihydroazeto[2′,3′:4,5]seleno[2,3-*b*]quinoline

Solid, mp. 292°C; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (ppm): 4.79 (1H, s, -Se-CH-), 5.70 (1H, s, -N-CH-C), 7.29–8.55 (9H, m, Ar-H); [M+], 385. Calcd. (%) for $C_{18}H_{11}ClN_2OSe$: C; 56.05, H; 2.87, N; 7.26, Se; 20.47, Found: C; 56.09, H; 2.89, N; 7.23, Se; 20.43.

2e. 1-(4-Nitrophenyl)-2a,7b-dihydroazeto[2′,3′:4,5]seleno[2,3-*b*]quinoline

Solid, mp. 288°C; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (ppm): 4.70 (1H, s, -Se-CH-), 5.68 (1H, s, -N-CH-C), 7.34–8.60 (9H, m, Ar-H). [M+], 396. Calcd. (%) for $C_{18}H_{11}N_3O_3Se$: C; 54.56, H; 2.80, N; 10.60, Se; 19.93, Found: C; 54.52, H; 2.83, N; 10.63, Se; 19.95.

4. Antimicrobial activity

The in vitro antimicrobial activity was carried out against 24 h old cultures of three bacteria by disk diffusion method [33] using ampicillin as the reference. Compounds **2a**–**e** were tested against Gram-positive bacteria (*Staphylococcus aureus, Micrococcus roseus*) and Gram-negative bacteria (*Escherichia coli*). The compounds were tested at a concentration of 0.001 mol/ml in DMF against all organisms. The zone of inhibition was compared with the standard drug after 24 h of incubation at 25°C and measured in mm. Results are reported in **Table 1**, and it was found that compounds **2d** and **2e** were highly active against *S. aureus* and *M. roseus*

Compound number	Microorganisms		
	S. aureus	*M. roseus*	*E. coli*
Ampicillin	20	22	22
2a	5	7	5
2b	4	4	4
2c	4	5	4
2d	13	16	10
2e	14	15	9

Zone of inhibition was expressed in mm.
Highly active +++ (inhibition zone >12 mm); moderately active ++ (inhibition zone 9–12 mm); slightly active + (inhibition zone 6–9 mm); and inactive (inhibition zone <6 mm).

Table 1.

*Antimicrobial activity tests of dihydroazeto[2′,3′:4,5]seleno[2,3-*b*]quinolines (**2a–e**).*

(Gram-positive) and moderately active against *E. coli* (Gram-negative), and compound **2c** was slightly active against *M. roseus* and *E. coli*. Compound **2e** was slightly active against *S. aureus* and *M. roseus*, and compounds **2a** and **2b** were slightly active against *M. roseus.* Other compounds were all inactive against these three pathogenic microorganisms. Hence, further studies in these compounds are planned to obtain clinically useful agents.

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