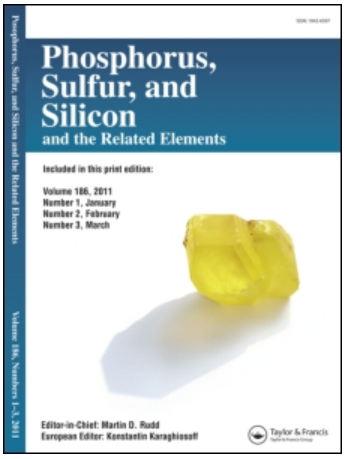

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Tangali R. Ravikumar Naik[a]; Halehatty S. Bhojya Naik[a]; Halehatty R. Prakash Naik[a]; M. Raghavendra[a]; S. Ramesha[a]

[a] Department of P. G. Studies and Research in Industrial Chemistry, School of Chemical Sciences, Kuvempu University, Shankaraghatta, India

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Synthesis of Novel 2-Seleno-1,8-naphthyridines Derivatives

Tangali R. Ravikumar Naik, Halehatty S. Bhojya Naik, Halehatty R. Prakash Naik, M. Raghavendra, and S. Ramesha
Department of P. G. Studies and Research in Industrial Chemistry, School of Chemical Sciences, Kuvempu University, Shankaraghatta, India

Synthesis of series of new 2-phenyl-3-(2-seleno-1,8-naphthyridin-3-yl)-2,3,3a,6-tetrahydro-5H-pyrazolo[3,4-d][1,3]thiazol-5-ones (4a–e) has been reported. The replacement of halogen with NaHSe in the substituted 2-chloro-3-formyl-1,8-naphthyridi afforded 2-seleno-3-formyl-1,8-naphthyridins (2a–e). The reaction between (2a–e)and 1,3-thiazolidine-2,4-dione produced corresponding derivatives of substituted compounds (3a–e), which on reflux with phenyl hydrazine in DMF to generate (4a–e), with good to excellent yields. Structure of newly synthesized compounds were established based on elemental analysis, IR, 1H NMR, and mass spectral data.

Keywords 2-selenonaphthyridines; naphthyridies; phenyl hydrazine; thiazolidine

INTRODUCTION

The functionalized naphthyridine derivatives have found a widespread application in the field of antibiotic, diagnostic, chemotherapy, and infectious diseases of humans including AIDS. Some of new 1,8-naphthyridne derivatives has also been patented as growth regulators fungicides, bactericides, herbicides, insecticides, and nemathocides of new generation.[1–4]

On the other hand, organoselenium compounds had substantially greater bioavailability and less toxicity than that of inorganic selenium.

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Address correspondence to Halehatty S. Bhojya Naik, Department of P. G. Studies and Research in Industrial Chemistry, School of Chemical Sciences, Kuvempu University, Shankaraghatta 577 451, India. E-mail: hsb_naik@rediffmail.com

Recent report[5] shows that, the micronutrient, selenium has potential anticarcinogenic activity of fused compounds such as selenocyanate,[6] triphenylselenonium, and diphenylselenide[7] have also been shown to be inhibitory in different tumor models. The condensed fused quinoline derivatives containing selenium atom and studies for their DNA binding, cytotoxic, anticancer activities.[8–10] Therefore, the development of organoselenium compounds with higher anticarcinogenic efficacy but better tolerance continues to be a priority in chemotherapy research.

Further, a large number of thiazolidinones are reported in literature for their biological activities such as anticonvulsant,[11] antiinflammatory,[12] hypnotic,[13] amoebicidal,[14] analgesic,[15] anti AIDS,[16]etc. 4-Thiazolidinone derivatives substituted at 2, 3, 4 or 5 positions are antidiabetic drugs.[17] Similarly Pyrazole derivatives are also reported to possess antifungal,[18] antidiabetic,[19] herbicidal,[20] antifertility,[21] sedative,[22] and antimicrobial activities,[23] and so on.

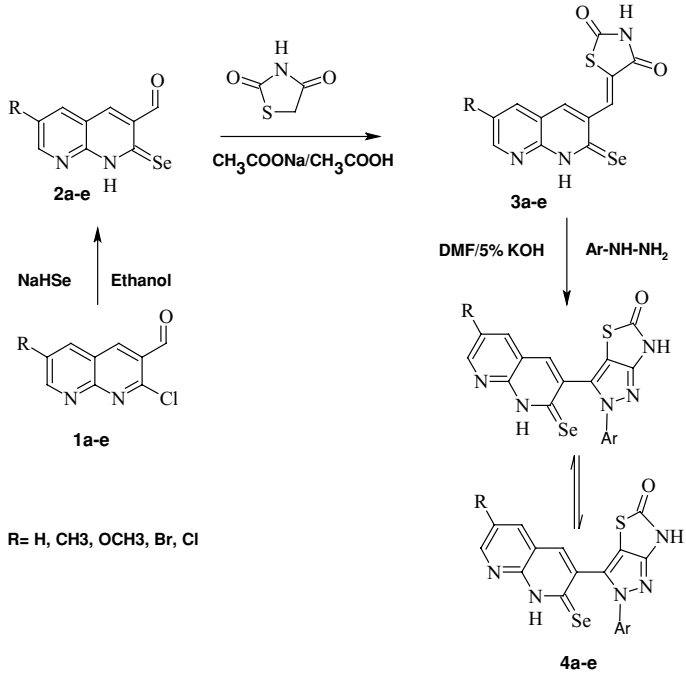
Hence, in view of the biological importance of these moieties and in continuation of our interest in the synthesis of novel heterocyclic framework,[24] we synthesized substituted 2-phenyl-3-(2-seleno-1,8-naphthyridin-3-yl)-2,3,3a,6-tetrahydro-5H-pyrazolo[3,4-d][1,3]thiazol-5-ones **(4a-e)** in good to excellent yield.

RESULTS AND DISCUSSION

The synthesized naphthyridine derivatives (**4a–e**) has include bioactive compounds like sulfur and selenium, which render them valuable pharmacological activities as mentioned earlier and they are a useful material in drug research and also naphthyridines might afford in better yields opening a chance for their DNA binding and antitumour activities.

2-chloro-3-formyl-1,8-naphthyridin was submitted to react with NaHSe in ethanol to obtained 85–90% yields of 2-seleno-3-formyl-1,8-naphthyridin **2a**. The IR spectra displayed bands at 1634 cm^{-1} (-C=Se), 3280 cm^{-1} (-NH) and 1690 cm^{-1} (-C=O). Its ^1H NMR spectra showed singlet at δ 13.4 for (-NH), δ10.56 for (-CHO), multiplet at 7.10–7.80. The obtained 2-seleno-3-formyl-1,8-naphthyridin **2a** treated with 1,3-thiazolidine-2,4-dione in the presence of glacial acetic acid and fused sodium acetate to offered **3a**. However, in contrast, 5-[(2-seleno-1,8-naphthyridin-3-yl)methylidene]-1,3-thiazolidine-2,4-dione **3a** up on reaction with excess of phenyl hydrazine in DMF solvent in a short reaction time afforded the products in a quantitative yield which were characterized as 2-phenyl-3-(2-seleno-1,8-naphthyridin-3-

yl)-2,3,3a,6-tetrahydro-5H-pyrazolo[3,4-d][1,3]thiazol-5-ones **4a** from their spectral data. Thus, IR spectrum of **4a** showed characteristic absorption at 1728 cm^{-1} (-C=O) for thiazolidinone ring, 1170 cm^{-1} (-N-N). Its ^1H NMR spectrum showed singlet at δ13.2 for (-NH) (toutomeric form) and absence of aldehydic proton at δ 10.56 ppm and its mass spectra with the m/z value at 428 (M+2).



SCHEME 1 2-phenyl-3-(2-seleno-1,8-naphthyridin-3-yl)-2,3,3a,6-tetrahydro-5H-pyrazolo[3,4-d][1,3]thiazol-5-ones.

EXPERIMENTAL SECTION

Melting points were determined in an open capillary tube with a Buchi melting point apparatus and are uncorrected. Elemental analyses were carried out using Perkin-Elmer 240C CHNS-analyzer. IR spectra were recorded on a FT-IR spectrophotometer.^1H NMR spectra was run in (DMSO-d_6) solvent at 300 MHz and 75 MHz on a NMR spectrophotometers (chemical shifts in δ ppm). Mass spectra were recorded on a LC MS Mass spectrometer. The absorption spectral studies were carried out by Ultraviolet-visible spectrophotometer.

General Procedure for the Synthesis of 2-Seleno-3-formyl-1,8-naphthyridines (2a)

A mixture 2-chloro-3-formyl-1,8-naphthyridine (1.91 g, 1 mmol) and freshly prepared solution of sodium hydrogen selenide were taken in a round bottom flask in ethanol (20 ml). The reaction mixture was refluxed for 2–3 hrs at 80–90°C, the completion of reaction was monitored by TLC eluting the phase ethyl acetate: carbon tetrachloride (70:30), cooled, the reaction mixture was poured in to crushed ice and made acidified with dil (4N HCl). The product was filtered and washed with water, dried, and was pure enough for further use, recrystallized from excess alcohol. The same procedure was used for the synthesis of other compounds (**2b–e**).

General Procedure for the Synthesis of 1,3-Thiazolidine-2,4-dion+

An ethanolic solution of thiourea (7.6 g, 0.5 mmol) and chloroacetic acid (3.8 g 0.6 mmol) was refluxed for 4–5 h. Then it was allowed to cool. The separated solid was filtered and washed with cold ethanol. The obtained hydrochloride was dissolved in boiling water (60 ml) after 24 h the separated crystals was filtered and refluxed for 1–2 h in aqueous KOH (20%, 15 ml). The reaction mixture was cooled and poured into dilute acetic acid (1:1, 50 ml). The precipitated solid was filtered and recrystallized from ethanol.

General Procedure for the Synthesis of 5-[(2-Seleno-1,8-naphthyridin-3-yl)methylidene]-1,3-thiazolidine-2,4-dione (3a)

Compound **2a** (1.185 g, 0.05 mmol), glacial acetic acid 30 ml, fused sodium acetate (0.589g, 0.05 mmol) and 1,3-thiazolidine-2,4-dione (0.05 mmol) were refluxed for 5–6 hrs at 80–90°C, the completion of reaction was monitored by TLC eluting the phase ethyl acetate: carbon tetrachloride (80:20), After cooling, reaction mixture was slowly poured into crushed ice and yellow solid obtained was filtered and washed with ethanol. The crude solid mass was recrystallized from glacial acetic acid. The same procedure was used for the synthesis of other compounds (**3b–e**).

General Procedure for the Synthesis of 2-Seleno-3-formyl-1,8-naphthyridines (4a)

An equimolar amount of compound **3a** (1.68 g, 0.05 mmol) and phenyl hydrazine (5.4 ml, 0.05 mmol) were dissolved in DMF with constant

stirring. To this stirred solution, 5% KOH (4 ml) was added dropwise during 20–30 min, and the reaction mixture was refluxed for 6–7 h at 80–90°C, the completion of reaction was monitored by TLC eluting the phase ethyl acetate: carbon tetrachloride (80:20), After cooling, the reaction mixture was poured in to crushed ice. The solid product so obtained was filtered, washed, dried, and crystallized from glacial acetic acid. The same procedure was used for the synthesis of other compounds (**4b–e**).

3-(2-Selenoquinolin-3-yl)-2-phenyl-2,6-dihydro-5H-pyrazolo[3,4-d][1,3]thiazol-5-one (4a)

Yellow solid. Yield 75%; m.p. 233°C; FT-IR (KBr): 1725 (C=O) cm^{-1}, 1170 (-N-N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ (ppm) = 13.02 (s, 1H, NH), 7.10–8.22 (m, 10H, Ar-H), Mass, m/z; 428 ($M^{\cdot+2}$). Elemental analysis (%): calcd., for $C_{18}H_{13}N_5OSSe$: C; 50.71, H; 3.07, N; 10.43 Found: C; 50.69, H; 3.06, N; 10.40.

6-Methyl 3-(2-selenoquinolin-3-yl)-2-phenyl-2,6-dihydro-5H-pyrazolo[3,4-d][1,3]thiazol-5-one (4b)

Yellow solid. Yield 70%; m.p. 208°C; FT-IR (KBr): 1728 (C=O) cm^{-1}, 1175 (-N-N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ (ppm) = 13.10 (s, 1H, NH), 7.00–8.05 (m, 9H, Ar-H), 2.85 (s, 3H, -CH_3), Mass, m/z; 442 ($M^{\cdot+2}$). Elemental analysis (%): calcd. for $C_{19}H_{15}N_5OSSe$: C; 51.82, H; 3.43, N; 15.90 Found: C; 51.80, H; 3.41, N; 15.88.

6-Methoxy 3-(2-selenoquinolin-3-yl)-2-phenyl-2,6-dihydro-5H-pyrazolo[3,4-d][1,3]thiazol-5-one (4c)

Yellow solid. Yield 70%; m.p. 216°C; FT-IR (KBr): 1720 (C=O) cm^{-1}, 1168 (-N-N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ (ppm) = 12.90 (s, 1H, NH), 7.05–8.10 (m, 9H, Ar-H), 3.90 (s, 3H, -O-CH_3), Mass, m/z; 458 ($M^{\cdot+2}$). Elemental analysis (%): calcd. for $C_{19}H_{15}N_5O_2SSe$: C; 50.00, H; 3.31, N; 15.35 Found: C; 49.98, H; 3.30, N; 15.33.

6-Bromo 3-(2-selenoquinolin-3-yl)-2-phenyl-2,6-dihydro-5H-pyrazolo[3,4-d][1,3]thiazol-5-one (4d)

Yellow solid. Yield 65%; m.p. 210°C; FT-IR (KBr): 1718 (C=O) cm^{-1}, 1185 (-N-N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ (ppm) = 13.20 (s, 1H, NH), 7.00–8.02 (m, 8H, Ar-H), Mass, m/z; 507 ($M^{\cdot+2}$). Elemental analysis (%): calcd., for $C_{18}H_{12}BrN_5OSSe$: C; 42.79, H; 2.39, N; 13.86 Found: C; 42.77, H; 2.38, N; 13.87.

6-Chloro 3-(2-selenoquinolin-3-yl)-2-phenyl-2,6-dihydro-5H-pyrazolo[3,4-d][1,3]thiazol-5-one (4e)

Yellow solid. Yield 65%; m.p.215°C; FT-IR (KBr): 1690 (C=O) cm^{-1}, 1173 (-N-N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ (ppm) = 13.05 (s, 1H, NH), 7.05–8.10 (m, 8H, Ar-H), Mass, m/z; 462 ($M^{\cdot+2}$). Elemental analysis (%): calcd., for $C_{18}H_{12}ClN_5OSSe$: C; 46.92, H; 2.62, N; 15.20 Found: C; 46.90, H; 2.61, N; 15.17.

CONCLUSIONS

In conclusion, we have successfully developed a facile convenient method, a new access to different class of biological importance of 2-seleno-3-formyl-1,8-naphthyridines by a simple methodology. These moieties have the potential to provide the basis for some biological importance.

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