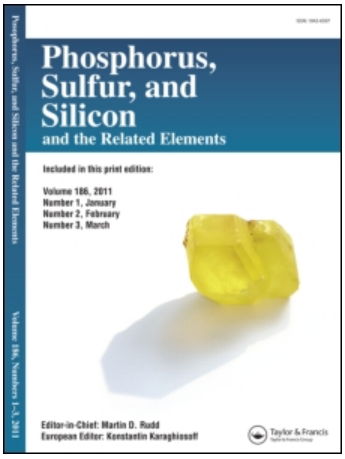

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Selenium Containing Heterocycles: Synthesis and Pharmacological Activities of Some New Selenolo[2,3-b]quinoline Derivatives and Related Pentacyclic Systems

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SELENIUM CONTAINING HETEROCYCLES: SYNTHESIS AND PHARMACOLOGICAL ACTIVITIES OF SOME NEW SELENOLO[2,3-b]QUINOLINE DERIVATIVES AND RELATED PENTACYCLIC SYSTEMS

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A new series of selenolo[2,3-b]quinoline, pyrimido[4′,5′:4,5]selenolo[2,3-b]quinoline, pyrimido[4′,5′:4,5]selenolo[2,3-b]-[1,2,4′triazolo[1,5-c]quinoline, and pyrimido[4′,5′:4,5] selenolo[2,3-b][1,2,4]triazolo[4,3-c]quinoline derivatives were prepared starting from diquinolinyl diselenide or 3-cyano-4-methylquinoline-2(1H)selenone with chloro acetonitrile or chloro acetamide. Elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data confirmed the structure of the newly synthesized compounds. In addition, the most active compounds were tested for their acute toxicity. Moreover, some of the tested compounds were screened for their antibacterial and antifungal activities. The minimum inhibitory concentration (MIC) of the most active compounds was 100 mg mL^{-1}.

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 Analgesic; anti-inflammatory; antimicrobial activities; pyrimidoselenolo quinolines; pyrimidoselenolo triazolo quinolines; quinolines

INTRODUCTION

Quinoline derivatives are widely used as antimalarial, antifungal, antibacterial, and antileishmanial agents, in addition to their antiarrhythmic activities.[1–5] In addition, the selenium atom plays a key role in the mode of action of such proteins, a role which cannot be played by its closest relative, sulfur.[6] Introduction of selenium into organic compounds often permits modification of their chemical properties and biological activities.[7,8] Moreover, organoselenium compounds have been found to function as antioxidants, chemoprotectors, apoptosis inducers, and chemopreventors in several organs such as the brain, liver, skin, colon, lung, and prostate.[9] Previous work in our laboratory described the synthesis of

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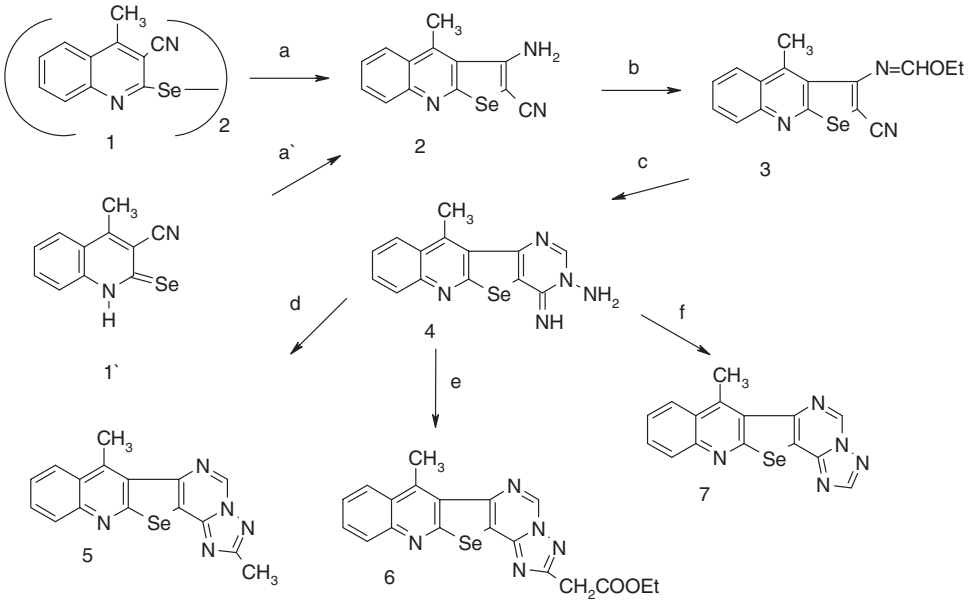
selenolo[2,3-*c*]pyridazine and selenolo[2,3-*b*]quinoline derivatives, several of which possess significant anti-inflammatory and analgesic activities with antimicrobial effects.[10,11] Linearly fused tetracyclic heterocycles have been reported and have become very important in recent years due to their close resemblance to the antitumor alkaloid ellipticine.[12] To increase the biological activities of the quinoline moiety by introducing selenium functionality, a convenient method for the synthesis of a novel pentacyclic condensed quinoline system is reported. The synthetic method involves successive building up of selenophene, pyrimidine, and triazole rings on a quinoline ring employing 3-cyanoquinolin-2(1H)-selenones **1′** or diquinolinyl diselenide derivatives **1** with chloro acetonitrile or chloro acetamide.

RESULTS AND DISCUSSION

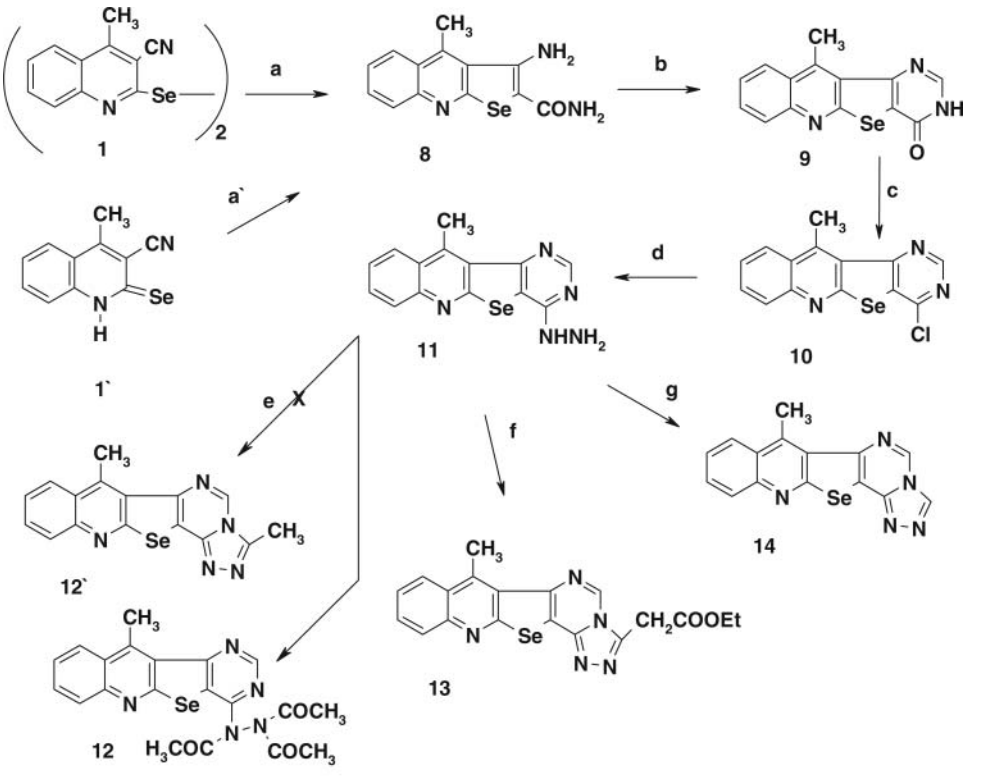
Nitrile compound **2** and amide compound **8** were used to prepare products **5–7**, structurally isomeric with **12–14**. Treatment of **2** with triethyl orthoformate led to the formation of ethoxymethylene amino derivative **3**, which reacted with hydrazine hydrate to furnish 3-amino-3,4-dihydro-4-imino-11-methylpyrimidine-[4′,5′:4,5]selenolo-[2,3-*b*]quinoline **4**. Heating of compound **4** with acetic anhydride afforded the 2,7-dimethylpyrimido[4′,5′:4,5]selenolo[2,3-*b*]-1,2,4-triazolo[1,5-c]quinoline **5**, while with diethylmalonate it provided ethyl 7-methylpyrimido-[4′,5′:4,5]selenolo[2,3-*b*]-1,2,4-triazolo[1,5-*c*]quinoline-2-acetate **6**. In the same manner, when compound **4** reacted with triethyl orthoformate, it gave the 7-methylpyrimido[4′,5′:4,5]selenolo[2,3-*b*]-1,2,4-triazolo[1,5-*c*]quinoline **7** (Scheme 1).

The IR spectra of the final compounds **4**, **5**, **6**, and **7** exhibited characteristic bands at 3150, 3200, 3330 cm^{-1} ($NHNH_2$) for compound **4**, and 1613–1617 cm^{-1} (>C=N) for compounds **5** and **7**. For compound **6**, the IR spectrum exhibited a characteristic band



Scheme 1 a=i) $NaBH_4$/EtOH/ ii) $ClCH_2CN$/NaOEt; á=$ClCH_2CN$/DMF/KOH
b=$CH(OEt)_3$/Ac_2O/reflux;
c=$NH_2NH_2XH_2O$(85%)/dioxan/Stirring rt;
d,e,f=Ac_2O,diethylmalonate, triethylortho formate/reflux

at 1734 cm^{-1} due to a (COOEt) group. ^1H NMR spectra of compounds **3**, **4**, **5**, **6**, and **7** displayed a quartet and triplet-like signals at δ: 4.47 (for CH_2) and 1.40 (for CH_3), corresponding to the protons of ethoxy group (OCH_2CH_3) in compound **3**, and δ: 1.25 (for CH_3), 4.10 (for CH_2) for compound **6**. For compounds **5** and **7**, the ^1H NMR spectra in TFA showed the most important signals at δ 8.93–9.35 (for CH-pyrimidine) and 4.03–4.15 (for CH_3-quinoline). Further confirmation of the precursor compound **3** was through the ^{13}C NMR spectrum. The signals obtained were all in a good agreement with the proposed structure. The most important peaks of compound **3** are δ 219.5 (−N=CH−O), 211.5, 190.0, 132.6, 131.3, 128.3 and 125.4 (Aryl), 69.1 (CH_2 and CH_3), 14.3 (CH_3 of quinoline). In the ^{13}C NMR spectra for compound **6**, the most important peaks are δ 170.5 (C=O-ester), 160.0 (N=CH-triazol ring), 157.0 (N=CH-pyrimidine ring), 132.5, 131.3, 128.3, 125.4 (Aryl), 119.1 (C-Se), 62.6 (OCH_2), 35.3 (O−CH_2), 14.3 (CH_3 of quinoline), 14.0 (CH_3-ester). The ^{13}C NMR spectrum for compound **13** is approximately the same value as in compound **6**. In the ^{13}C NMR for compounds **5**, **7**, **12**, and **14**, peaks were not observed as a result of the solubility of these compounds in TFA and slight solubility in DMSO. Another confirmation of the final products **3–7** was by mass spectra, where compounds **3–7** exhibited molecular ion peaks at m/z, (%) 343 (M^+, 100%), 329 (M^+, 41%), 351 (M^+, 100%), 425 (M^+, 100%), and 339 (M^+, 100%), respectively.



Scheme 2 Synthesis of compounds **9–11, 13**, and **14**.

Reaction of **8** with triethyl orthoformate in acetic acid gave further fused pyrimido[4′,5′:4,5]selenolo[2,3-*b*]quinoline derivative **9**. Treatment of compound **9** with phosphorus oxychloride led to the 4-chloropyrimidine derivative **10**, which underwent other nucleophilic substitution upon treatment with hydrazine hydrate, affording the 4-hydrazino derivative **11**. The hydrazine compound **11** was used as a precursor to new pentacyclic systems. Thus, treatment with acetic anhydride, diethyl malonate, and triethyl orthoformate gave 11(N,N′-triacetylhydrazino)-4-methylpyrimido[4′,5′:4,5]selenolo[2,3-*b*] quinoline **12** rather than the expected compound 3,7-dimethylpyrimido-[4′,5′:4,5]selenolo [2,3-*b*]-1,2,4-triazolo[4,3-*c*]quinoline **12′**, ethyl 7-methylpyrimido[4′,5′:4,5]selenolo[2,3-*b*]-1,2,4-triazolo[4,3-*c*]quinoline-3-acetate **13**, and 7-methyl-pyrimido[4′,5′:4,5]selenolo [2,3-*b*]-1,2,4-triazolo[4,3-*c*]quinoline **14**, respectively (Scheme 2).

The **IR** spectra of the final products **12–14** exhibited characteristic bands at 1600–1629 cm^{-1} (>C=N). For compound **12**, the IR spectrum exhibited characteristic band at 1737 cm^{-1} due to (C=O of three acetyl groups). For compound **13**, the IR spectrum exhibited characteristic band at 1735 cm^{-1} due to the (COOEt) group. The ^{1}H NMR spectra of compounds **12–14** displayed a quartet and triplet-like signals at δ: 4.21 (for CH_2) and 1.27 (for CH_3), corresponding to the protons of ester group ($COOCH_2CH_3$) in compound **13** and 7.93 (CH-pyrimidine). For compound **14**, CH-pyrimidine shifted to δ 10.55 due to TFA. The ^{1}H NMR spectrum of **12** at δ: 2.21, 2.63, 2.74 and 3.17 for (3 peaks CH_3-acetyl group and CH_3-quinoline). Mass spectra of compounds **12–14** exhibited molecular ion peaks at m/z, (%) 454 (M^+-1, 100%), 353 (M^+, 41%), 339 (M^+, 51%), respectively.

CONCLUSIONS

We have presented the straightforward synthesis of variously substituted derivatives of new pentacyclic system (**5**, **6**, **7**, **13**, and **14**) starting from diquinolinyl diselenide (**1**) or 3-cyano-4-methylquinoline-2(1H)selenone (**1′**) with chloro acetonitrile or chloro acetamide. From the thermodynamic point of view, the relative stability of the two isomeric structures **6**, **7** seems to be more stable than **13**, **14**. Applications of these new pentacyclic derivatives (**5**, **6**, **7**, **13**, and **14**) were investigated for their anti-inflammatory and analgesic activities,[13,14] which showed activity comparable to the standard drug indomethacin, and have no analgesic activity except compound **13**. LD_{50}[15] of tested compounds **6**, **7**, **13**, and **14** were nontoxic at doses up to 50 mg/25 g mice. Moreover compounds **7**, **13**, and **14** have no antimicrobial activities against all species of bacteria and fungi, except for compound **7**, which showed a strong effect against *Escherichia coli*, and compound **13**, which showed a moderate effect against *Staphylococcus aureus*. On the other hand, the compounds show no effect against the tested fungal species with the exception of compound **13**, which showed strong effect against *Candida albicans*, and compound **14**, which showed moderate activity against *Staphylococcus aureus*. The minimum inhibitory concentration (MIC) of the most active compounds (**7** and **13**) was 100 mg mL^{-1}.The experiments also reveal that compounds **7** and **13** are completely inactive at 50 mg mL^{-1} against all the tested fungi and bacteria.[16] (See the Supplemental Materials, Tables S1–S3, available online.)

EXPERIMENTAL

Melting points were determined using a Kofler melting point apparatus (C. Reichert, Vienna, Austria) and are uncorrected. IR (KBr) spectra were recorded on a Pye-Unicam SP3-100 instrument (Pye Unicam Ltd., Cambridge, England) and FT-IR Nicolet 6700

Thermo Electronic Corporation (Thermo Fisher Scientific, Inc., USA). ^{1}H NMR spectra were obtained on a Varian EM 390 (Varian Inc., Palo Alto, CA, USA) using tetramethylsilane as an internal reference. Mass spectra were recorded on a JEOL-JMS-AX 600 (JEOL, Tokyo, Japan) at Assiut University, Assiut, Egypt. M^+ ions are given for ^{80}Se unless otherwise stated; the mass spectra were recorded via EI^+ inlet. ^{13}C NMR spectra were recorded on a GEMINI-200 NMR200 at Cairo University. Elemental analyses were obtained on an Elementar Vario EL 1150C analyzer (Heraeus, Germany). The purity of the compounds was checked by TLC. Experimental details of the biological testing can be found in the Supplemental Materials.

Compounds **1**, **1′**, **2**, and **8** were prepared as previously described.[11]

Ethyl N-(2-Cyano-4-methylselenolo[2,3-b]quinoline-3-yl)methanimidate 3

Crystallized from ethanol, mp = 150–152°C, yield (76%). IR (cm^{-1}) 2200 (CN); 1640 (C=N). ^{1}H NMR (δ, ppm): (DMSO-d_6): 7.65–8.26 (m, 4H Ar-H); 7.65 (s, 1H N=CH); 4.47 (q, 2H CH_2); 3.37 (s, 3H, CH_3-quinoline); 1.40 (t, 3H CH_3); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 219.5 (−N=CH−O), 211.5, 190.0, 132.6, 131.3, 128.3, 125.4 (Aryl), 111.1 (C−CN), 72.6, 69.1 (CH_2 and CH_3), 14.3 (CH_3 of quinoline), mass spectrum of compound **3** ($C_{16}H_{13}N_3OSe$) exhibited molecular ion peak at m/z, (%) 343 (M^+, 100%), and the other important fragments were observed at 344 (M^+ +1, 22%), 345 (M^+ +2, 23%), 295 [39], 287 [59], 140 [68], 77 [11]. Anal: calc. for $C_{16}H_{13}N_3OSe$ (342.28): C, 56.14; H, 3.84; N, 12.28. Found: C, 56.12; H; 3.64, N, 12.43.

3-Amino-3,4-dihydro-4-imino-11-methylpyrimidine [4′,5′:4,5]selenolo[2,3-b]quinoline 4

The iminoether **3** (3.4 g, 10 mmol) was suspended in dioxane (10 mL), then hydrazine hydrate (88%, 2 mL) was added, and the reaction mixture was stirred at room temperature for 3 h. The solid product that formed was collected and recrystallized from dioxane as pale yellow crystals (2.5 g, 77%), mp >300°C.

IR: ν_{max} 3150, 3200 3330 cm^{-1} ($NHNH_2$). ^{1}H NMR (DMSO-d_6): δ 9.15 (s, 1H, NH), 8.08 (s, 1H, CH-pyrimidine), 7.25–7.87 (m, 4H, Ar-H), 5.89 (s, 2H, NH_2), 2.73 (s, 3H, CH_3), MS: *m/z* (%) 329 (M^+ 100). Anal: calc. for C14H11N5Se (328.21): C, 51.23; H, 3.38; N, 21.34. Found: C, 51.01; H, 3.12; N, 21.06.

2,7-Dimethylpyrimido[4′,5′:4,5]selenolo[2,3-b]-1,2,4-triazolo[1,5-c]quinoline 5

Compound **4** (3.2 g, 10 mmol) was heated under reflux for 6 h. in acetic anhydride (20 mL). The precipitate that formed while hot was collected and recrystallized from dioxane as brown crystals (2.7 g, 79%), mp > 300°C. IR: νmax 1617 cm^{-1} (C=N).^{1}H NMR (TFA): 8.91 (s, 1H, CH-pyrimidine), 7.25–7.91 (m, 4H, Ar-H), 3.45 (s, 3H, CH_3-triazole), 3.37 (s, 3H, CH_3-Quinoline), MS: *m/z* (%) 351 (M+, 100%). Anal: calc. for $C_{16}H_{11}N_5Se$ (352.28): C, 54.55; H, 3.15; N, 19.88. Found: C, 54.21; H, 3.00; N, 19.77.

Ethyl 7-methylpyrimido[4′,5′:4,5]selenolo[2,3-b]-1,2,4-triazolo[1,5-c]quinoline-2-acetate 6

Compound **4** (3.2 g, 10 mmol) was heated under reflux with diethyl malonate (15 mL) for 6 h. The reaction mixture was then cooled and triturated with ethanol (15 mL). The solid that separated was collected and recrystallized from ethanol as yellow crystals (3 g, 72%), mp 252–254°C. IR: ν_{max} 1734 cm^{-1} (C=O-ester). ^1H NMR (DMSO-d_6): δ 8.08 (s, 1H, CH-pyrimidine), 7.25–7.68 (m, 4H, Ar-H) 4.10 (q, 2H, CH_2-ester), 3.37 (s, 3H, CH_3-Quinoline), 1.25 (t, 3H, CH_3-ester); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 170.5 (C=O-ester), 160.0 (N=CH-triazol ring), 157.0 (N=CH-pyrimidine ring), 132.5, 131.3, 128.3, 125.4 (Aryl), 119.1 (C-Se), 62.6, (OCH_2), 35.3 (O-CH_2), 14.3 (CH_3 of quinoline), 14.0 (CH_3-ester). MS: *m/z* (%) 425 (M+, 100%). Anal: calc. for $C_{19}H_{15}N_5O_2Se$ (424.35): C, 53.77; H, 3.57; N, 16.51. Found: C, 53.65; H, 3.56; N, 16.29.

7-Methylpyrimido[4′,5′:4,5]selenolo[2,3-b]-1,2,4-triazolo[1,5-c]quinoline 7

Compound **4** (3.2 g, 10 mmol) was heated under reflux for 6 h in acetic anhydride (20 mL). The precipitate that formed while hot was collected and recrystallized from DMF/H_2O as brown crystals (2.5 g, 78%), mp >300°C. IR: ν_{max} 1613 cm^{-1} (C=N). ^1H NMR (TFA): 9.10 (s, 1H, CH-triazole), 8.75 (s, 1H, CH-pyrimidine), 7.35–7.91 (m, 4H, Ar-H), 3.37 (s, 3H, CH_3-Quinoline). MS: *m/z* (%) 339 (M+, 100%). Anal: calc. for $C_{15}H_9N_5Se$ (338.25): C, 53.27; H, 2.68; N, 20.71. Found: C, 53.11; H, 2.45; N, 20.55.

4-Methylpyrimido[4′,5′:4,5]selenolo[2,3-b]quinoline 11(1H)-one 9

This compound was prepared by the reaction of **8** (3 g, 10 mmol) with excess triethyl orthoformate (10 mL) and a few drops of acetic acid. After 10 min, the pale yellow crystals are formed while hot and collected. They were recrystallized from DMF/water as yellow crystals (2.5 g, 83%), mp >300°C. IR: ν_{max} 3150 (NH), 3050 (CH-aromatic), 1651 cm^{-1} (C=O). ^1H NMR (TFA): δ 8.91 (s, 1H, CH-pyrimidine), 8.58 (m, 4H, Ar-H), 3.95 (s, 1H, NH), 3.37 (s, 3H, CH_3-Quinoline). MS: *m/z* (%): 315.26 (M+ 8%). Anal: calc. for $C_{14}H_9N_3OSe$ (314.22): C, 53.51; H, 2.89; N, 13.38. Found: C, 53.29; H, 2.68; N, 13.36.

11-Chloro-4-Methylpyrimido[4′,5′:4,5]selenolo[2,3-b]quinoline 10

A suspension of compound **9** (3.1 g, 10 mmol) in excess phosphorus oxychloride (20 mL) was heated under reflux for 3 h. The cooled reaction mixture was poured on an ice bath. The precipitated solid was collected and recrystallized from ethanol as yellow crystals (2.7 g 84%); mp 250–252°C. IR (ν_{max} cm^{-1}):1640 (C=N). ^1H NMR (DMSO-d_6): 9.01 (s, 1H, CH-pyrimidine), 7.35–8.01 (m, 4H, Ar-H), 3.37 (s, 3H, CH_3-Quinoline)). MS: *m/z* (fragment, 335.25 (M^+ 44%). Anal: calc. for $C_{14}H_8ClN_3Se$ (332.71): C, 50.54; H, 2.43; N, 12.63; Cl, 10.67. Found: C, 50.35; H, 2.34; N, 12.41; Cl 10.55.

11-Hydrazino-4-methylpyrimido[4′,5′:4,5]selenolo[2,3-b]quinoline 11

The chloro compound **10** (3.3 g, 10 mmol) in ethanol (20 mL) was heated under reflux for 2 h with hydrazine hydrate (88%, 4 mL, 40 mmol). The product that formed

while hot was collected and recrystallized from dioxane to give yellow crystals; yield (2.6 g, 81%), mp > 300°C. IR: νmax 3100, 3300, 3400 cm^{-1} ($NHNH_2$). ^1H NMR (TFA): δ 8.05–9.01 (m, 4H, Ar-H), 7.19 (s, 1H, CH-pyrimidine), 4.01 (s, 3H, CH_3-Quinoline). MS: *m/z* (%) 329.3 (M^+ +100%). Anal: calc. for $C_{14}H_{11}N_5Se$ (328.26): C, 51.22; H, 3.38; N, 21.34. Found: C, 51.10; H, 3.30; N, 21.11.

11(N,N′-Triacetylhydrazino)-4-methylpyrimido[4′,5′:4,5]selenolo [2,3-b]quinoline 12

Compound **11** (3.2 g, 10 mmol) in acetic anhydride (20 mL) was heated under reflux for 6 h. The precipitate that formed while hot was collected and recrystallized from dioxane as orange crystals (3 g, 68%), mp >300°C. IR: νmax 1673, 1737 (3 acetyl group). ^1H NMR (TFA): δ 8.91 (s, 1H, CH-pyrimidine), 8.75 (m, 4H, Ar-H), 3.37 (s, 3H, CH_3-Quinoline), 2.21 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 2.74 (s, 3H, CH_3). MS: m/z (%) 455 (M^+ + 88%).Anal: calc. for $C_{20}H_{17}N_5O_3Se$ (454.38): C, 52.86; H, 3.78; N, 15.42. Found: C, 52.69; H, 3.56; N, 15.22.

Ethyl 7-Methylpyrimido[4′,5′:4,5]selenolo[2,3-b]-1,2,4-triazolo[4,3-c]quinoline-3-acetate 13

The hydrazine **11** (3.2 g, 10 mmol) was heated under reflux with diethyl malonate (15 mL) for 6 h. The reaction mixture was then cooled and triturated with ethanol (15 mL). The solid that separated was collected and recrystallized from ethanol as pale yellow crystals (3.5 g, 85%), mp 246–248°C. IR (ν_{max} cm^{-1}): 1735 cm^{-1} (C=O-ester). ^1H NMR (DMSO-d_6): δ 8.01 (s, 1H, CH-pyrimidine), 7.45–7.93 (m, 4H, Ar-H), 4.10 (q, 2H, CH_2-ester), 3.51 (s, 3H, CH_3-Quinoline), 1.15 (t, 3H, CH_3-ester). ^{13}C NMR (DMSO-d_6, 50 MHz): approximately the same value as in compound **6**.MS: *m/z* (%) 425.39 (M^+, 0.2), 353 (425.39-$C_3H_5O_2$, 100%). Anal: calc. for $C_{19}H_{15}N_5O_2Se$ (424.35): C, 53.77; H, 3.57; N, 16.51. Found: C, 53.58; H, 3.44; N, 16.34.

7-Methylpyrimido[4′,5′:4,5]selenolo[2,3-b]-1,2,4-triazolo[4,3-c]quinoline 14

Compound **11** (3.2 g, 10 mmol) was heated under reflux in triethyl orthoformate (10 mL) for 4 h. A solid product that formed while hot was collected and recrystallized from DMF/H_2O as brown crystals (2.5 g, 76%), mp > 300°C. IR: ν_{max} 1620 cm^{-1} (C=N). ^1H NMR (TFA): 10.55 (s, 1H, CH-triazole), 8.79 (s, 1H, CH-pyrimidine), 8.10–8.55 (m, 4H, Ar-H), 4.01 (s, 3H, CH_3-Quinoline) MS: *m/z* (%) 339.29 (M^+, 51). Anal: calc. for $C_{15}H_9N_5Se$ (338.25): C, 53.27; H, 2.68; N, 20.71. Found: C, 53.17; H, 2.42; N, 20.54.

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