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SELENIUM-CONTAINING HETEROCYCLES

3*. SYNTHESIS AND REACTIONS OF SELENOLO-[2,3-*b*]PYRIDINE DERIVATIVES AND RELATED FUSED TRICYCLIC SYSTEMS

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A new series of pyrido[3',2':4,5]selenolo[3,2-d]pyrimidine derivatives is reported. The structures of the newly synthesized compounds were elucidated by elemental analyses and spectral data (IR, ^{1}H and ^{13}C NMR, MS).

Keywords: fused pyridines, pyridines, pyridoselenolopyrimidines.

Selenium has long been recognized as a dietary antioxidant and is now known to be an essential component of the active sites of several enzymes, including glutathione peroxidase [2] and thioredoxin reductase, which catalyze reactions essential for the protection of cellular components against oxidative and radical damage [3]. Moreover, previous work in our laboratory describes the synthesis of pyrimidoselenolo-[2,3-*b*]quinoline [4] and pyrimidoselenolo[2,3-*c*]pyridazine derivatives [5] and indicates that certain compounds possess significant anti-inflammatory and analgesic activities with strong fungicidal effects. Furthermore, in Part 1 [6] and Part 2 [1] we published the synthesis of selenolo[2,3-*b*]pyridine, pyrido[3',2':4,5]selenolo-[3,2-*d*]pyrimidine, 2,4-dimethyl-7,8-dihydropyrrolo[1,2-*a*]pyrido[3',2':4,5]selenolo[3,2-d]pyrimidin-10(6H)-one, 7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine, 7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidine-2,4(1H,3H)-dithione, 7,9-dimethylpyrido[3',2':4,5]selenolo[2,3-*e*]tetrazolo[1,5-*c*]pyrimidine-6(5H)thione, 9,11-dimethylpyrido[3',2':4,5]selenolo[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine, 7,9-dimethylpyrido[3',2':4,5]selenolo[2,3-*e*]imidazo[1,2-*c*]pyrimidine, and 10,12-dimethylpyrido[3",2":4',5']selenolo-[3',2':4,5]pyrimido[1,6-*a*]pyrimidine derivatives. Prompted by these observations and in continuation of our work we report herein new classes of fused tri- and tetracyclic systems containing the selenolo[2,3-*b*]pyridine fragment in the hope that members of these series may find interesting biological applications.

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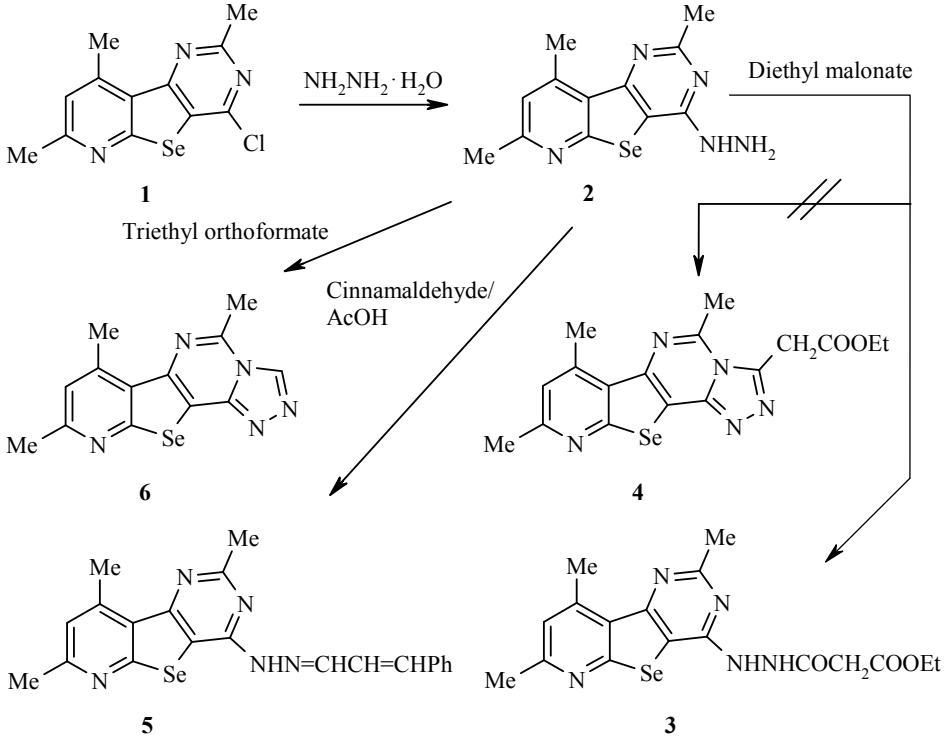
The starting 4-chloro-2,7,9-trimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidine (**1**) was obtained by previously described procedures [1, 6] using acetic anhydride instead of formic acid. Compound **1** reacted with hydrazine hydrate to give 4-hydrazino-2,7,9-trimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidine (**2**), which was allowed to react with diethyl malonate and afforded ethyl 3-oxo-3-[2-(2,7,9-trimethylpyrido[3',2':4,5]-selenolo[3,2-*d*]-pyrimidin-4-yl)hydrazino]propanoate (**3**) instead of ethyl (5,7,9-trimethylpyrido[3',2':4,5]-selenolo[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-yl)acetate (**4**). Compound **2** reacted with cinnamaldehyde in glacial acetic acid and triethyl orthoformate to give the corresponding cinnamaldehyde hydrazone **5** and 5,7,9-trimethylpyrido[3',2':4,5]selenolo[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (**6**), respectively (Scheme 1). The assigned structures of the newly synthesized compounds were consistent with their spectral properties and elemental analyses.

Scheme 1



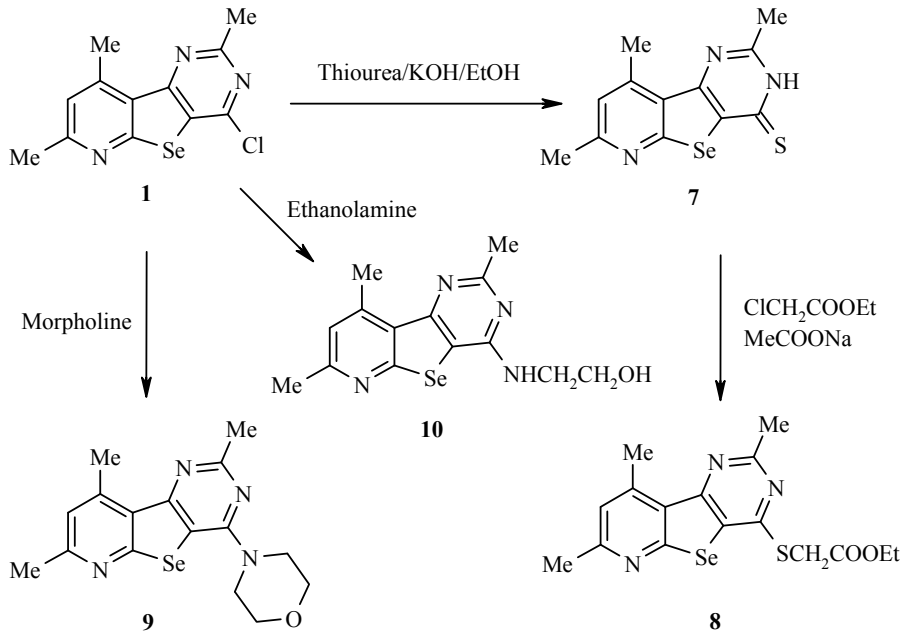
1 **2** **6** **4** **5** **3**

Chloropyrimidine **1** underwent nucleophilic substitution reactions with thiourea, morpholine, and ethanolamine. The first reaction led to the formation of 2,7,9-trimethylpyrido[3',2':4,5]selenolo[3,2-*d*]-pyrimidine-4(3H)-thione (**7**), which on treatment with ethyl chloroacetate in the presence of anhydrous potassium carbonate produced ethyl 2-(2,7,9-trimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidin-4-ylsulfanyl)-acetate (**8**). Other reactions gave 2,7,9-trimethyl-4-morpholinopyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidine (**9**) and 2-[(2,7,9-trimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidin-4-yl)amino]ethanol (**10**), respectively (Scheme 2).

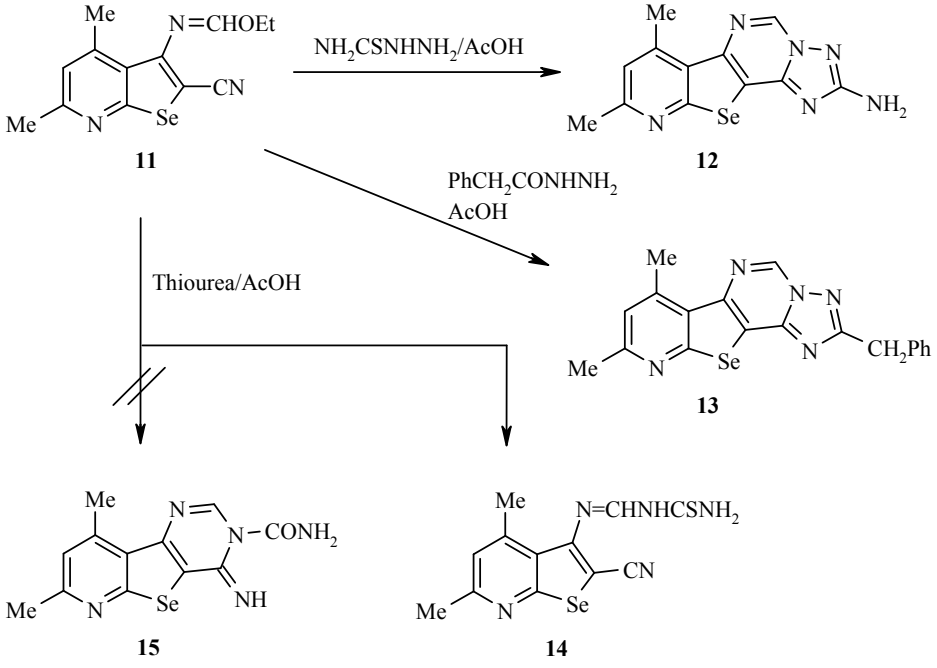
Some other tri- and tetracyclic systems were prepared starting from the previously described [5, 6] ethoxy-methylideneamino derivative **11** which reacted with thiosemicarbazide, phenylacetohydrazide in acetic acid, and thiourea to yield 7,9-dimethylpyrido[3',2':4,5]selenolo[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine-2-amine (**12**), 2-benzyl-7,9-di-methylpyrido[3',2':4,5]selenolo[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (**13**), and {[(2-cyano-4,6-di-methyl-selenolo[2,3-*b*]pyridin-3-yl)imino]methyl}thiourea (**14**), respectively, rather than the expected pyrimidine ring-containing tricyclic system **15** (Scheme 3).

Finally, we used compound **16** as a precursor to prepare new heterocyclic systems containing selenium *via* treatment of compound **16** with diethyl malonate and ethyl acetoacetate in the presence of glacial acetic acid, which afforded ethyl 2-(7,9-dimethyl-4-oxo-3,4-dihydropyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidin-2-yl)acetate (**17**) and 7,9-dimethyl-2-(2-oxopropyl)pyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidin-4(3H)-one (**18**) (Scheme 4).

Scheme 2



Scheme 3

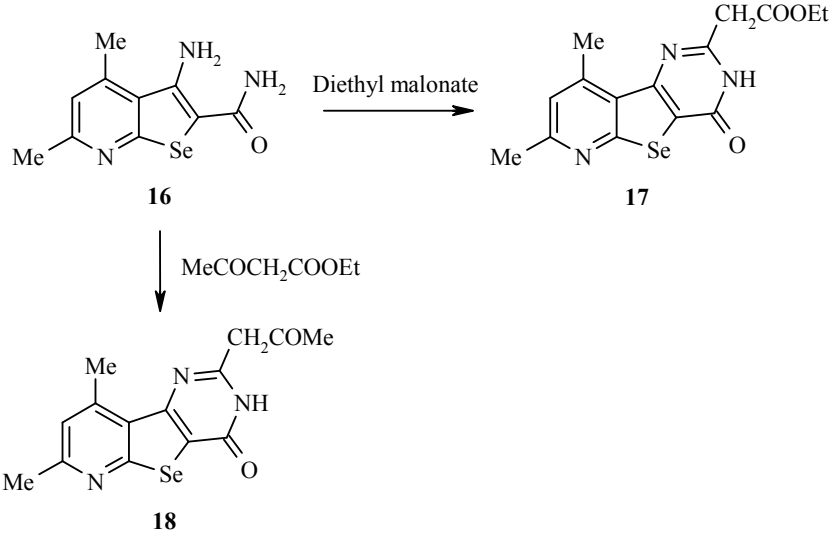


EXPERIMENTAL

Melting points were determined using a Kofler melting point apparatus and are uncorrected. IR spectra were recorded on a Pye-Unicam SP3-100 instrument in KBr pellets. The mass spectra (EI, 70 eV, ion source temperature 210ºC) were recorded on a Jeol JMS600 instrument. ^{1}H NMR spectra were obtained on a JEOL LA

400 spectrometer (400 MHz) in $CDCl_3$ (compound **1**) or deuterated trifluoroacetic acid using TMS as internal standard. Elemental analyses were obtained on an Elementar Vario EL 1150C analyzer. Purity of the compounds was checked by TLC on Silufol UV-254 plates with 1:1 acetone–benzene as the eluent using UV light for visualization.

Scheme 4



Compounds **11** and **16** were prepared as previously described [1, 6].

4-Chloro-2,7,9-trimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidine (1). A mixture of 2,7,9-trimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidin-4(3H)-one (1 g, 3.41 mmol) in excess phosphorus oxychloride (20 ml) was heated under reflux for 3 h. The cooled reaction mixture was poured onto ice. The precipitated solid was collected and recrystallized from ethanol to give white crystals, yield 0.75 g (70 %); mp 186-188°C. IR spectrum, ν, cm^{-1}: 1640 (C=N). ^{1}H NMR spectrum, δ, ppm: 7.70 (1H, s, CH pyridine); 3.41 (3H, s, CH_3); 3.12 (3H, s, CH_3); 2.96 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 314 $[M+1]^+$ (40); 313 $[M]^+$ (100). Found, %: C 46.18; H 3.01; Cl 11.03; N 13.21. $C_{12}H_{10}ClN_3Se$. Calculated, %: C 46.40; H 3.24; Cl 11.41; N 13.53.

4-Hydrazino-2,7,9-trimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidine (2). The chloro compound **1** (2.0 g, 6.4 mmol) in ethanol (20 ml) was heated under reflux for 2 h with hydrazine hydrate (99 %, 4 ml, 40 mmol). The product that precipitated while hot was collected and recrystallized from dioxane to give white crystals, yield 1.70 g (60%); mp >300ºC. IR spectrum, ν, cm^{-1}: 3400, 3300, 3100 ($NHNH_2$). ^{1}H NMR spectrum, δ, ppm: 7.55 (1H, s, CH pyridine); 3.41 (3H, s, CH_3); 3.12 (3H, s, CH_3); 2.96 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 307 $[M]^+$ (100). Found, %: C 46.88; H 4.25; N 22.51. $C_{12}H_{13}N_5Se$. Calculated, %: C 47.07; H 4.28; N 22.87.

Ethyl 3-Oxo-3-[2-(2,7,9-trimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidin-4-yl)hydrazino]-propanoate (3). The hydrazino compound **2** (1 g, 3.15 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 formed was collected and recrystallized from ethanol to give pale-yellow crystals, yield 1.02 g (75%); mp 224–226ºC. IR spectrum, ν, cm^{-1}: 1740 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.90 (1H, s, CH pyridine); 4.30 (2H, q, J = 7.1, CH_2); 3.41 (3H, s, CH_3); 3.32 (3H, s, CH_3); 2.83 (3H, s, CH_3); 1.46 (3H, t, J = 6.9, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 421 $[M]^+$ (10), 307 $[M-C_5H_7O_3]^+$ (100). Found, %: C 48.33; H 4.59; N 16.28. $C_{17}H_{19}N_5O_3Se$. Calculated, %: C 48.58; H 4.56; N 16.66.

2,7,9-Trimethyl-4-[2-(3-phenylprop-2-en-1-ylidene)hydrazinyl]pyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidine (5). The hydrazino compound **2** (1 g, 3.15 mmol) was heated under reflux with cinnamaldehyde

(2 ml) in 10 ml of acetic anhydride for 3 h. The reaction mixture was then cooled, and the precipitated solid was collected and recrystallized from ethanol to give yellow crystals, yield 0.34 g (25%); mp 240-242ºC. IR spectrum, ν, cm^{-1}: 3200 (NH). ^{1}H NMR spectrum, δ, ppm: 7.95 (1H, s, CH pyridine); 7.15-7.85 (8H, m, H Ar + 3CH); 3.41 (3H, s, CH_3); 3.32 (3H, s, CH_3); 2.84 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 421 $[M + 1]^+$ (39). Found, %: C 59.98; H 4.23; N 16.52. $C_{21}H_{19}N_5Se$. Calculated, %: C 60.00; H 4.56; N 16.66.

5,7,9-Trimethylpyrido[3',2':4,5]selenolo[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (6). The hydrazino compound **2** (1 g, 3.15 mmol) was heated under reflux in triethyl orthoformate (10 ml) for 4 h. The solid product that formed while hot was collected and recrystallized from dioxane to give white crystals, yield 0.8 g (78%); mp >300ºC. IR spectrum, ν, cm^{-1}: 1620 (C=N). ^{1}H NMR spectrum, δ, ppm: 9.77 (1H, s, CH triazole); 7.95 (1H, s, CH pyridine); 3.41 (3H, s, CH_3); 3.32 (3H, s, CH_3); 3.13 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 316 $[M-1]^+$ (100). Found, %: C 49.33; H 3.46; N 22.08. $C_{13}H_{11}N_5Se$. Calculated, %: C 49.38; H 3.51; N 22.15.

2,7,9-Trimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidine-4(3H)-thione (7). Compound **1** (1.0 g, 3.22 mmol) and thiourea (0.24 g, 3.16 mmol) were heated under reflux in ethanol (20 ml) for 3 h, and then 20 ml of 10% sodium hydroxide was added to the reaction solution followed by further reflux for 0.5 h. The solution was then filtered hot, and the cooled filtrate was acidified with acetic acid, giving a yellow precipitate which was collected and recrystallized from aqueous DMF to give yellow crystals, yield 0.89 g (90%); mp >300ºC. IR spectrum, ν, cm^{-1}: 3400 (NH). ^{1}H NMR spectrum, δ, ppm: 7.95 (1H, s, CH pyridine); 3.41 (3H, s, CH_3); 3.32 (3H, s, CH_3); 2.85 (3H, s, CH_3). Found, %: C 46.34; H 3.38; N 13.46; S 10.12. $C_{12}H_{11}N_3SSe$. Calculated, %: C 46.76; H 3.60; N 13.63; S 10.40.

Ethyl (2,7,9-Trimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidin-4-ylsulfanyl)acetate (8). Ethyl chloroacetate (0.4 g, 3.25 mmol) was added to the thione **7** (1 g, 3.23 mmol) and anhydrous potassium carbonate (0.5 g, 5.1 mmol) in DMF (20 ml). The mixture was heated under reflux for 2 h and after cooling was poured into ice-water, giving a white precipitate which was collected and recrystallized from ethanol to give white crystals, yield 0.83 g (65%); mp 160-162ºC. IR spectrum, ν, cm^{-1}: 1740 (C=O ester). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.94 (1H, s, CH pyridine); 3.95 (2H, q, J = 7.0, CH_2); 3.71 (2H, s, SCH_2); 3.41 (3H, s, CH_3); 3.32 (3H, s, CH_3); 2.84 (3H, s, CH_3); 1.55 (3H, t, J = 7.0, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 397 $[M+2]^+$ (19), 395 $[M]^+$ (9). Found, %: C 48.40; H 4.21; N 10.57; S 7.98. $C_{16}H_{17}N_3O_2SSe$. Calculated, %: C 48.73; H 4.35; N 10.66; S 8.13.

2,7,9-Trimethyl-4-morpholinopyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidine (9). A mixture of compound **1** (1 g, 3.22 mmol) and morpholine (4 ml) was gently heated under reflux for 2 h, and the reaction mixture was triturated with ethanol (15 ml) and then left to cool. The precipitated solid was collected and recrystallized from ethanol to give brown crystals, yield 0.93 g (80 %); mp 243–245ºC. IR spectrum, □, cm^{-1}: 1640 (C=N). ^{1}H NMR spectrum, δ, ppm: 7.95 (1H, s, CH pyridine); 4.35–4.53 (8H, m, CH_2 morpholine); 3.41 (3H, s, CH_3); 3.32 (3H, s, CH_3); 2.85 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 362 $[M]^+$ (4). Found, %: C 53.02; H 4.97; N 15.34. $C_{16}H_{18}N_4OSe$. Calculated, %: C 53.19; H 5.02; N 15.51.

2-[(2,7,9-Trimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidin-4-yl)amino]ethanol (10). A mixture of compound **1** (1 g, 3.22 mmol) in ethanolamine (4 ml) was gently heated under reflux for 2 h, and the reaction mixture was triturated with ethanol (15 ml) and then left to cool. The precipitated solid was collected and recrystallized from ethanol to give white crystals, yield 0.81 g (75%); mp >300ºC. IR spectrum, ν, cm^{-1}: 3400 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.95 (1H, s, CH pyridine); 4.31 (2H, t, J = 7.1, CH_2); 3.54 (3H, s, CH_3); 3.31 (3H, s, CH_3); 2.95 (3H, s, CH_3); 2.80 (2H, t, J = 7.1, CH_2). Mass spectrum, *m/z* (I_{rel}, %): 336 $[M]^+$ (78). Found, %: C 50.00; H 4.67; N 16.34. $C_{14}H_{16}N_4OSe$. Calculated, %: C 50.15; H 4.81; N 16.71.

7,9-Dimethylpyrido[3',2':4,5]selenolo[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine-2-amine (12). A mixture of compound **11** (1.5 g, 5 mmol) and thiosemicarbazide (5 mmol) in acetic acid (20 ml) was heated under reflux for 3 h. The precipitate formed while hot was collected and recrystallized from DMF/water, yield 0.7 g (45%); mp >300ºC. IR spectrum, ν, cm^{-1}: 3400, 3200 (NH_2). ^{1}H NMR spectrum, δ, ppm: 8.73 (1H, s, CH pyrimidine); 7.80 (1H, s, CH pyridine); 3.41 (3H, s, CH_3); 3.34 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 318 $[M]^+$ (13). Found, %: C 45.22; H 3.17; N 26.34. $C_{12}H_{10}N_6Se$. Calculated, %: C 45.44; H 3.18; N 26.49.

2-Benzyl-7,9-dimethylpyrido[3',2':4,5]selenolo[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (13). A mixture of compound **11** (1.5 g, 5 mmol) and 2-phenylacetohydrazide (5 mmol) in acetic acid (20 ml) was heated under reflux for 3 h. The precipitate formed while hot was collected and recrystallized from DMF/water, yield 0.93 g (60%); mp >300ºC. IR spectrum, ν, cm^{-1}: 1640 (C=N). ^{1}H NMR spectrum, δ, ppm: 9.50 (1H, s, CH pyrimidine); 7.82 (1H, s, CH pyridine); 7.30–7.85 (5H, m, H Ph); 4.64 (2H, s, CH_2); 3.41 (3H, s, CH_3); 3.20 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 395 $[M+1]^+$ (41), 394 $[M]^+$ (100). Found, %: C 58.05; H 3.59; N 17.63. $C_{19}H_{15}N_5Se$. Calculated, %: C 58.17; H 3.85; N 17.85.

{[(2-Cyano-4,6-dimethylselenolo[2,3-*b*]pyridin-3-yl)imino]methyl}thiourea (14). A mixture of compound **11** (1.5 g, 5 mmol) and thiourea (5 mmol) in acetic acid (10 ml) was heated under reflux for 2 h. The precipitate formed on cooling was collected and recrystallized from acetic acid to give yellow crystals, yield 1.42 g (87%); mp 242-244ºC. IR spectrum, ν, cm^{-1}: 3410 (NH), 3400, 3300 (NH_2), 2200 (CN). ^{1}H NMR spectrum, δ, ppm: 7.80 (1H, s, CH pyridine); 7.15 (1H, s, N=CH); 3.41 (3H, s, CH_3); 3.22 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 337 $[M]^+$ (1). Found, %: C 42.55; H 3.09; N 20.53; S 9.22. $C_{12}H_{11}N_5SSe$. Calculated, %: C 42.86; H 3.30; N 20.83; S 9.54.

Ethyl 2-(7,9-Dimethyl-4-oxo-3,4-dihydropyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidin-2-yl)acetate (17). A mixture of compound **16** (1 g, 3.7 mmol) and diethyl malonate (2 ml) in 2 ml of acetic acid was heated under reflux for 3 h. The reaction mixture was cooled and the product that formed was collected and recrystallized from ethanol to give white needles, yield 0.67 g (50%); mp 190–193ºC. IR spectrum, ν, cm^{-1}: 3400 (NH), 1680 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.80 (1H, s, CH pyridine); 4.00 (2H, q, J = 7.1, CH_2); 3.65 (2H, s, CH_2); 3.41 (3H, s, CH_3); 3.23 (3H, s, CH_3); 1.28 (3H, t, J = 7.1, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 364 $[M-1]^+$ (73). Found, %: C 49.05; H 3.99; N 11.23. $C_{15}H_{15}N_3O_3Se$. Calculated, %: C 49.46; H 4.15; N 11.54.

7,9-Dimethyl-2-(2-oxopropyl)pyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidin-4(3H)-one (18). A mixture of compound **16** (1 g, 3.7 mmol) and ethyl acetoacetate (2 ml) in 2 ml of acetic acid was heated under reflux for 3 h. The reaction mixture was cooled and the product that formed was collected and recrystallized from ethanol to give white needles, yield 0.81 g (60%); mp 280–282ºC. IR spectrum, ν, cm^{-1}: 3400 (NH), 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.80 (1H, s, CH pyridine); 3.71 (2H, s, CH_2); 3.41 (3H, s, CH_3); 3.25 (3H, s, CH_3); 1.55 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 335 $[M]^+$ (60). Found, %: C 49.99; H 3.89; N 12.35. $C_{14}H_{13}N_3O_2Se$. Calculated, %: C 50.31; H 3.92; N 12.57.

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