Selenium containing heterocycles: Part 1. Synthesis of some new substituted pyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidines and related fused tetracyclic systems

Shams H. Abdel-Hafez*, Ragaa A. Ahmed, Mohamed A. Abdel-Azim and Khairy M. Hassan

Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt

New series of selenolo[2,3-*b*]pyridine, pyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidine, 7,8-dihydro-2,4-dimethylpyrrolo [1,2-*a*]pyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidin-10(6*H*)-one and 7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-*d*][1,2,4] triazolo[4,3-*c*]pyrimidine derivatives were synthesised from 3-cyano-4,6-dimethylpyridine-2(1*H*)-selenone (**1**). Spectroscopic (IR, ^{1}H, MS) of the newly synthesised compounds are reported.

Keywords: fused pyridines, pyridines, selenophenes, 1,2,4-triazoles, pyrroles

Pyridine derivatives occupy a unique position in medicinal chemistry. Members of this class have been found to be protectors against gastric ulcers,[1] and coronary vasodilators and agents for the improvement of blood circulation.[2] In addition, the pyridine ring plays vital roles in fundamental metabolism.[3,4] Also, many pyridines are reported to be useful as herbicidal,[5] bactericidal,[6] fungicidal,[7] as well as pharmaceutical[8] materials. On the other hand, organoselenium compounds have attracted the attention of investigators owing to their unique properties and pharmaceutical applications.[9-14] Also organic selenium compounds have proven to be an important class of biologically active compounds as antioxidants,[15] antibacterial agents[16] and catalysts.[17] Considering the foregoing benefits, and in continuation of our efforts in the preparation of new heterocyclic systems containing selenium and/or sulfur moieties,[18-24] we aimed to combine the selenophene ring with the pyridine nucleus giving selenolo[2,3-*b*]pyridine derivatives in the hope that members of this series may find interesting biological applications.

Results and discussion

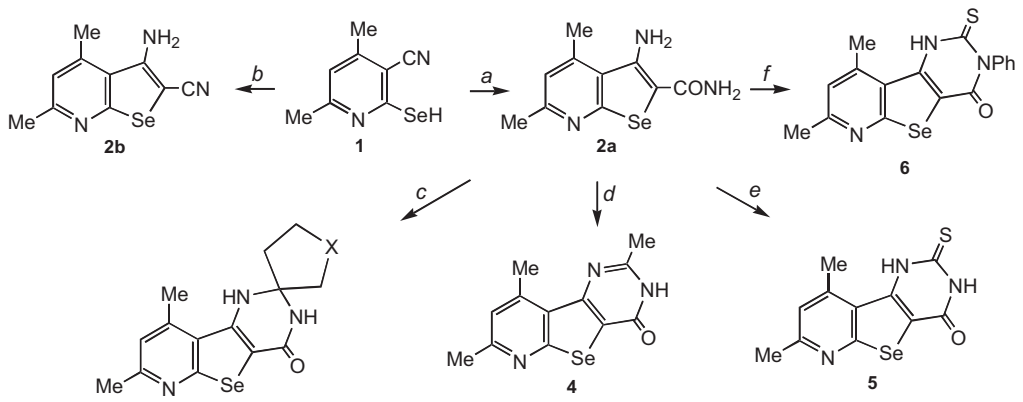
The starting 2-substituted-3-amino-4,6-dimethylselenolo[2,3-*b*]pyridines **2a**,**b** were readily obtained by previously described procedures.[23,25] Compound **2a** reacted with cycloalkanones, acetic anhydride, carbon disulfide, and phenyl isothiocyanate to give the pyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidine derivatives **3a**,**b**, **4**, **5** and **6** respectively (Scheme 1). The assigned structures of the newly synthesised compounds were consistent with their spectral properties and elemental analysis.

The reactivity of the thio and imino groups of compound **5** was tested by alkylation with ethyl and propyl iodide which afforded derivatives **7** or **8** respectively (Scheme 2). It is noteworthy that the alkylation occurred both at the S atom and the N(3) atom, because of the reactivity of the thiolate and the cyclic imide groups under the reaction conditions (DMF/K_2CO_3).

Reactions of **2a** with formic acid, aromatic aldehydes, and chlorobutyryl chloride gave further fused selenolopyridine derivatives **9**, **10a–c**, and **12** respectively (Scheme 3). The reaction of **2a** with 4-chlorobutyryl chloride was carried out under neat conditions and did not give the expected chloropropyl derivative **11** but instead provided the pyrrolo [1,2-*a*]pyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidine **12**. This result can be explained by formation of the intermediate pyrimidine derivative **11** followed by cyclisation to **12** with loss of HCl.

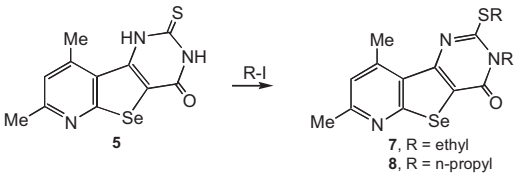
Treatment of compound **9** with phosphorus oxychloride led to the 4-chloro-7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-*d*] pyrimidine (**13**) (Scheme 4). This with thiourea gave the thione **14**. Upon treatment of compound **14** with ethyl chloroacetate in the presence of anhydrous potassium carbonate, the corresponding *S*-alkylated thiopyridoselenolopyrimidine derivative **15** was obtained.

The chloropyrimidine derivative **13** underwent other nucleophilic substitutions upon treatment with piperidine, morpholine and hydrazine hydrate affording the 4-substituted 7,9-dimethylpyrido[3'2':4,5]selenolo[3,2-*d*]pyrimidines **16a**,**b** and **17**. The hydrazino compound **17** was used as a precursor



Scheme 1

* Correspondent. E-mail: shams@aun.edu.eg



Scheme 2

to new tetracyclic systems. Thus, condensation with triethyl orthoformate led to the formation of the 1,2,4-triazolo-fused compound **18.** Compound **17** when heated with diethyl malonate gave ethyl 7,9-dimethylpyrido[3',2':4,5]selenolo[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine-3-acetate (**19**), and the related 3-methyl analogue **20** was obtained by the reaction of **17** with acetic anhydride (Scheme 5).

Finally, we used the nitrile **2b** to prepare products **23**–**25**, structurally isomeric with **18**-**20**. Upon treatment of **2b** with triethyl orthoformate led to the formation of ethoxymethylene amino derivative **21** which reacted with hydrazine hydrate furnished 3-amino-3,4-dihydro-4-imino-7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidine **22.** Heating of compound **22** with triethyl orthoformate afforded the pyridoselenolo[1,2,4]triazolopyrimidine derivative **23.** while with diethyl malonate it provided ethyl 7,9-dimethylpyrido[3',2':4,5]selenolo[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine-2-acetate (**24**). In the same manner, when compound **22** reacted with acetic anhydride it gave the 2-methyl analogue **25** (Scheme 6). It should be noted that products **23**–**25** were similar but not identical in physical and spectroscopic properties to compounds **18**–**20**, showing that interconversion by Dimroth rearrangement had not occurred under the conditions of their synthesis.

Experimental

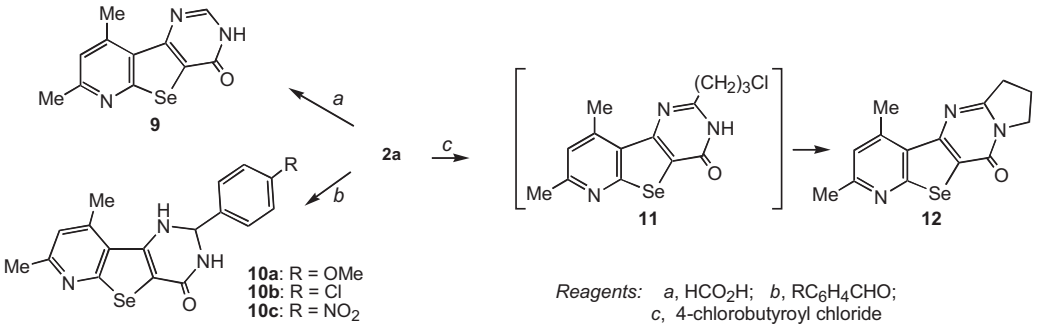
Melting points were determined using a Kofler melting point apparatus. IR spectra were recorded on a Pye-Unicam SP3-100 instrument in KBr. The mass spectra (EI, 70 eV, ion source temperature 210°C) were recorded on a Jeol JMS600 instrument. ^{1}H NMR spectra were obtained on a Varian spectrometer (90 MHz) using tetramethylsilane as internal reference. Elemental analyses were obtained on an Elementer Vario EL 1150C analyser. Purity of the compounds was checked by TLC.

Compounds **1** and **2a,b** were prepared as previously described.[23,25]

2-Spiro-substituted 7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-d]pyrimidin-4(3H)-one (**3a,b**)

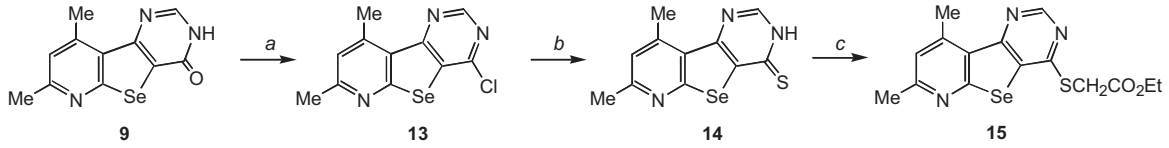
The amino-amide **2a** (2.68 g, 10 mmol) and cyclohexanone or cyclopentanone (10 mmol) in acetic acid (10 ml) were heated under reflux for 6 h. The solid product which separated on cooling was collected and recrystallised from dioxan.

Spirocyclopentane derivative **3a**: pale yellow crystals (2.63 g, 79%), m.p. 252–254°C. IR: ν_{max} 3150, 3300 (2NH), 3050 (CH-arom), 1640 cm^{-1}(C=O). ^{1}H NMR (DMSO-d$_6$): δ 7.0 (s, 1H, CH-pyridine), 8.0 (s, 1H, CONH), 6.0 (s, 1H, NH), 2.6 (s, 3H, CH_3), 2.8 (s, 3H,



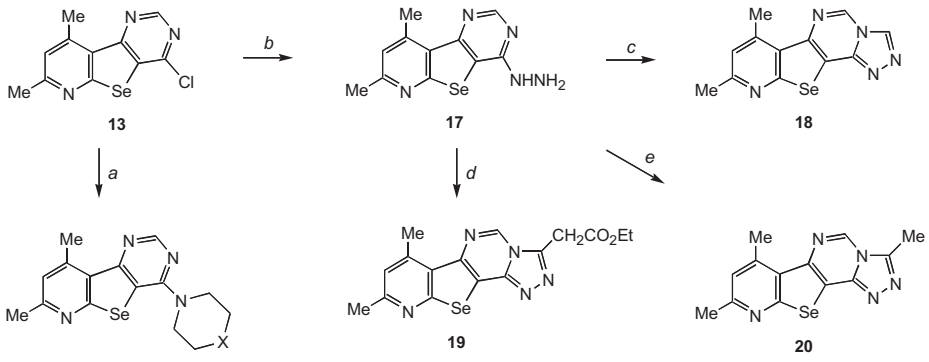
Reagents: *a*, HCO_2H; *b*, RC_6H_4CHO; *c*, 4-chlorobutyroyl chloride

Scheme 3



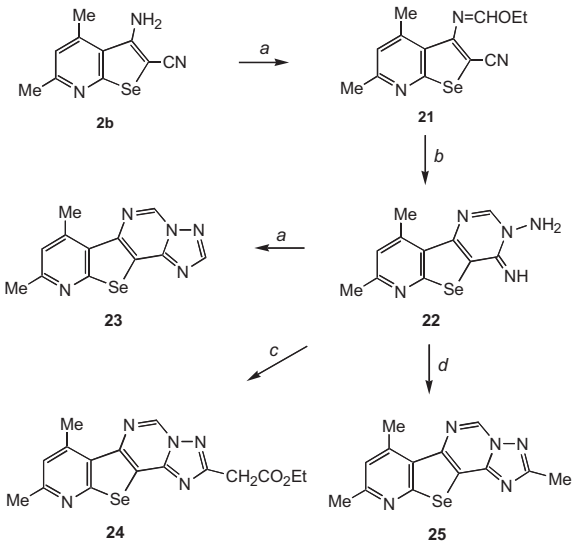
Reagents: *a*, $POCl_3$; *b*, thiourea; *c*, $ClCH_2CO_2Et$

Scheme 4



Reagents: *a*, piperidine, morpholine; *b*, hydrazine hydrate; *c*, $HC(OEt)_3$; *d*, diethyl malonate, *e*, Ac_2O

Scheme 5



Reagents: *a*, triethyl orthoformate; *b*, hydrazine hydrate; *c*, diethyl malonate, *d*, Ac_2O

Scheme 6

CH_3), 1.3–2.4 (m, 8H, 4 CH_2). MS: *m/z* (%) 335 (M^+, 68.5). Anal: calc. for $C_{15}H_{17}N_3OSe$ (334.3): C, 53.89; H, 5.08; N, 12.57. Found: C, 53.56; H, 4.97; N, 12.22%.

Spirocyclohexane derivative **3b**: Pale yellow crystals (2.85 g, 82%), m.p. 240°C. IR: ν_{max} 3150, 3250 (2NH), 3050 (CH-aromatic), 1620 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ 7.0 (s, 1H, CH-pyridine), 7.8 (s, 1H, CONH), 5.8 (s, 1H, NH), 2.6 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 1.2–2.2 (m, 10H, 5CH_2). MS: *m/z* (%) 349 (M^+, 68.3), 348 (M^+-H, 34.2). Anal: calc. for $C_{16}H_{19}N_3OSe$ (348.3) C, 55.17; H, 5.45; N, 12.06. Found: C, 55.36; H, 5.92; N, 11.75%.

2,7,9-Trimethylpyrido[3',2':4,5]selenolo[3,2-d]pyrimidin-4(3H)-one (**4**)

Compound **2a** (2.68 g, 10 mmol) was heated under reflux in acetic anhydride (10 ml) for 3 h. The product that formed on cooling was collected and recrystallised from aqueous DMF to give yellow crystals (1.54 g, 53%), m.p.: >300°C. IR: ν_{max} 3150 (NH), 3050 (CH-arom), 1640 cm^{-1} (C=O). ^1H NMR (TFA): δ 7.7 (s, 1H, CH-pyridine) 3.0 (s, 3H, CH_3), 3.2 (s, 3H, CH_3), 3.4 (s, 3H, CH_3-pyrimidine). MS: *m/z* (%) 293 (M^+, 100). Anal: calc. for $C_{12}H_{11}N_3OSe$ (292.2) C, 49.31; H, 3.76; N, 14.38. Found: C, 49.20; H, 3.49; N, 14.03%.

2,3-Dihydro-7,9-dimethyl-2-thioxopyrido[3',2':4,5]selenolo[3,2-d]pyrimidin-4(1H)-one (**5**)

Compound **2a** (2.68 g, 10 mmol) and carbon disulfide (5 ml) in pyridine (20 ml) were heated on water bath for 12 h. The solid product was collected and recrystallised from dioxan forming yellow crystals (1.33 g, 43%), m.p. >300°C. IR: ν_{max} 3400, 3100 (2NH), 1660 cm^{-1} (C=O). ^1H NMR (TFA): 7.5 (s, 1H, CH-pyridine), 3.0 (s, 3H, CH_3), 3.2(s, 3H, CH_3). MS: *m/z* (%): 311 (M^+, 100). Anal: calc. for $C_{11}H_9N_3OSSe$ (310.2) *Calcd.* C, 42.58; H, 2.90; N, 13.54; S, 10.32. Found: C, 42.58; H, 2.82; N, 13.43; S, 10.15%.

2,3-Dihydro-7,9-dimethyl-3-phenyl-2-thioxopyrido[3',2':4,5]selenolo[3,2-d]pyrimidin-4(1H)-one (**6**)

The amide **2a** (2.68 g, 10 mmol) in pyridine (15 ml) was heated with phenyl isothiocyanate (1.9 ml, 10 mmol) under reflux for 3 h. The solid product that separated while hot was recrystallised from dioxan as yellow crystals (2.24 g, 58%), m.p. >300°C. IR: ν_{max} 3300 (NH), 1660 cm^{-1} (C=O). ^1H NMR (TFA): δ 7.6–7.8 (m, 6H, CH-pyridine and ArH), 3.0 (s, 3H, CH_3), 3.2 (s, 3H, CH_3). MS: *m/z* (%) 387 (M^+, 49.4); 386 (M^+-1, 22.3). Anal: calc. for $C_{17}H_{13}N_3OSSe$ (386.34): C, 52.84; H, 3.36; N, 10.88; S, 8.29. Found: C, 52.42 H, 2.98; N, 10.53; S, 7.89%.

3-Alkyl-2-alkylthio-7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-d]pyrimidin-4(3H)-ones (**7**, **8**)

Compound **5** (3.1 g, 10 mmol) was stirred at room temperature in DMF containing anhydrous potassium carbonate (2.72 g, 20 mmol) with an excess of alkyl halide for 10 h. The reaction mixture poured onto ice-water giving a white precipitate which was collected and recrystallised from ethanol.

3-Ethyl-2-ethylthio compound (**7**): Obtained using ethyl iodide; white crystals (3.0 g, 82%), m.p. 152–154°C. ^1H NMR (DMSO-d_6): δ 7.2 (s, 1H, CH-pyridine), 3.3 (m, 4H, 2CH_2-ethyl), 3.0 (s, 3H, CH_3-pyridine), 2.6 (s, 3H, CH_3-pyridine), 1.5 (m, 6H, 2CH_3-ethyl). MS: *m/z* (%) 367 (M^+, 100). Anal: calc. for $C_{15}H_{17}N_3OSSe$ (366.35): C, 49.18; H, 4.64; N,11.47; S,8.74. Found: C, 49.39; H,4.31; N,11.21; S,8.98%.

3-Propyl-2-propylthio compound (**8**): Obtained using *n*-propyl iodide; white crystals (3.19 g, 81%), m.p. 172–174°C. ^1H NMR (DMSO-d_6): δ 7.2 (s, 1H, CH-pyridine), 1.3 (m. 6H, 2CH_3 propyl), 4.7 (m, 8H, S–CH_2, N-CH_2 and 2 CH_2), 2.6 (s, 3H, CH_3), 2.8 (s, 3H, CH_3). MS: *m/z* (%) 395 (M^+, 100). Anal: calc. for $C_{17}H_{21}N_3OSSe$ (394.4): C, 51.77; H, 5.32; N, 10.65; S, 8.12. Found: C, 51.54; H, 5.22; N, 10.53; S, 8.37%.

7,9-Dimethylpyrido[3',2':4,5]selenolo[3,2-d]pyrimidin-4(3H)-one (**9**)

This compound was prepared by the reaction of **2a** according to the above procedure which was described for compound **4,** using formic acid in place of acetic anhydride. It was recrystallised from dioxan-DMF as white crystals (1.77 g, 64%), m.p. >300°C. IR: ν_{max} 3150 (NH), 3050 (CH-aromatic), 1640 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ 7.3 (s 1H, CH-pyridine) 8.3 (s, 1H, CH-pyrimidine), 2.4 (s, 3H, CH_3), 2.8 (s, 3H, CH_3). MS: *m/z* (%): 279 (M^+, 100). Anal: calc. for $C_{11}H_9N_3OSe$ (278.2): C, 47.48; H, *3.23; N, 15.10. Found: C, 47.68; H, 3.14; N, 15.03%.*

2-Aryl-2,3-tetrahydro-7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-d]pyrimidin-4(1H)-ones (**10a–c**): *general procedure*

The amide **2a** (2.68 g, 10 mmol) was heated under reflux for 6 h in glacial acetic acid (10 ml) with the appropriate benzaldehyde (10 mmol). The product **10** that formed on cooling was collected and recrystallised from dioxan**.**

2-(4-Methoxyphenyl) compound (**10a**)**:** Prepared using 4-methoxybenzaldehyde. Yellow crystals (2.35 g., 61%), m.p. >300°C. IR: ν_{max} 3400 (NH), 3050 (CH-aromatic) 1660 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ 8.0 (s, 1H, CONH), 7.1 (s, 1H, CH-pyridine), 7.2–7.4 (m, 4H, ArH), 6.9 (s, 1H, 2-CH), 2.4 (s, 3H, CH_3), 2.8 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3). MS: *m/z* (%) 386 (M^+-H, 35.3). Anal: calc. for $C_{18}H_{17}N_3O_2Se$ (386.3): C, 55.95; H, 4.40; N, 10.88. Found: C, 55.46; H, 4.47; N, 11.13%.

2-(4-Chlorophenyl) compound (**10b**)**:** Prepared using 4-chlorobenzaldehyde. Yellow crystals (3.25 g, 83%), m.p. >300°C. IR: ν_{max} 3150 (NH), 1640 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ 8.4 (s, 1H, CONH), 7.0 (s, 1H, CH-pyridine), 7.2–7.4 (m, 4H, ArH), 5.8 (s, 1H, 2-CH), 2.5 (s, 3H, CH_3), 2.8 (s, 3H, CH_3). MS: *m/z* (%) 389 (M^+, 30.3); 390 (M^+–H, 100), 391 (M^+, 21.6). Anal: calc. for $C_{17}H_{14}ClN_3OSe$ (390.74): C, 52.24; H, 3.58; N, 10.75. Found: C, 51.94; H, 3.04; N, 10.43%.

2-(4-Nitrophenyl) compound (**10c**): Prepared using 4-nitrobenzaldehyde. Yellow crystals (3.45 g, 86%), m.p. >300 °C. IR: ν_{max} 3400, 3500 (2NH), 1640 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ 8.6 (s, 1H, CONH), 7.1 (s, 1H, CH-pyridine), 7.9–8.2 (m, 4H, ArH), 6.0 (s, 1H, 2-CH), 2.5 (s, 3H, CH_3), 2.8 (s, 3H, CH_3). MS: *m/z* (%) 401 (M^+-H, 40.8). Anal: calc. for $C_{17}H_{14}N_4O_3Se$ (401.3): C, 50.87; H, 3.49; N, 13.96. Found: C, 51.10; H, 3.46; N, 13.52%.

7,8-Dihydro-2,4-dimethylpyrido[3',2':4,5]selenolo[3,2-d]pyrrolo[1,2-a]pyrimidin-10(6H)-one (**12**)

The amino-amide **2a** (2.68 g, 10 mmol) was heated in 4-chlorobutyryl chloride (10 ml) on a water bath for 3 h. A solid product that formed on cooling was collected and recrystallised from ethanol-dioxan to give pale yellow crystals (2.73 g, 86%), m.p. 302–304°C. IR: ν_{max} 1640 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ 6.0 (s, 1H, CH-pyridine) 2.1 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 1.6 (m, 2H, CH_2-pyrrole), 2.8 (m, 4H, 2CH_2-pyrrole). MS: *m/z* (%) 319 (M^+, 12). Anal: calc. for $C_{14}H_{13}N_3OSe$ (318.24): C, 52.83; H, 4.08; N, 13.20. Found: C, 52.97; H, 4.42; N, 12.98%.

4-Chloro-7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-d]pyrimidine (**13**)

A suspension of compound **9** (2.78 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 recrystallised from ethanol as white crystals; yield: 2.638 g (89%); m.p. 140–142°C. IR (cm^{-1}):1640 (C=N). ^1H NMR ($CDCl_3$, ppm): 9.0 (s, 1H, CH-pyrimidine), 7.3 (s, 1H, CH-pyridine), 2.8 (s, 3H, CH_3), 3.0 (s, 3H, CH_3). MS: *m/z* (%): 297 (M^+, 100); 299 (M^+, 44). Anal: calc. for $C_{11}H_8ClN_3Se$ (296.62): C, 44.51; H, 2.69; N, 14.16. Found: C, 44.31; H, 2.63; N, 14.49.

7,9-Dimethylpyrido[3',2':4,5]selenolo[3,2-d]pyrimidine-4(3H)-thione (**14**)
Compound **13** (2.96 g, 10 mmol) and thiourea (0.76 g; 10 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 recrystallised from aqueous DMF as yellow crystals (2.65 g, 90%), m.p.>300°C. IR: ν_{max} 3400 cm^{-1} (NH). ^1H NMR (DMSO-d_6): 15.7 (s, 1H, SH) 8.5 (s, 1H, CH-pyrimidine), 7.2 (s, 1H, CH-pyridine), 2.6 (s, 3H, CH_3), 2.8(s, 3H, CH_3). MS: *m/z* (%) 295 (M^+, 100). Anal: calc. for $C_{11}H_9N_3Se$ (294.24): C, 44.89; H, 3.06; N, 14.28; S, 10.88. Found: C, 45.34; H, 3.28; N, 14.76; S, 10.52%.

Ethyl [(7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-d]pyrimidin-4-yl) thio]acetate (**15**)
Ethyl chloroacetate (1.23 g, 10 mmol) was added to the thione **14** (2.94 g, 10 mmol) and anhydrous potassium carbonate 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 recrystallised from ethanol giving white crystals (3.15 g, 83%), m.p. 162–164°C. IR: ν_{max} 1640 cm^{-1} (C=O ester). ^1H NMR (DMSO-d_6): δ 8.8 (s, 1H, CH-pyrimidine), 7.2 (s, 1H, CH-pyridine), 2.6 (s, 3H, CH_3), 2.9 (s, 3H, CH_3), 1.4 (t, 3H, ester CH_3), 4.5 (m, 4H, OCH_2, SCH_2). MS: *m/z* (%) 307 (M^+-COOEt, 100). Anal: calc. for $C_{15}H_{15}N_3O_2SSe$: C, 47.36; H, 3.94; N, 11.05; S, 8.42. Found: C, 46.98; H, 4.23; N, 10.88; S, 8.12%.

Aminodechlorination reactions: preparation of **16a, b**
A mixture of **13** (2.96 g, 10 mmol) in piperidine or morpholine (4 ml) was gently heated under reflux for 2 h, the reaction mixture was triturated with ethanol (15 ml) and than left to cool. The precipitated solid that formed was collected and recrystallised from ethanol.

7,9-Dimethyl-4-piperidinopyrido[3',2':4,5]selenolo[3,2-d] pyrimidine (**16a**): White crystals (2.93 g, 85%), m.p. 132–134°C. ^1H NMR (DMSO-d_6): δ 8.6 (s, 1H, CH-pyrimidine), 7.3 (s, 1H, CH-pyridine), 1.5 (m, 6H, $3CH_2$-piperidine), 2.8 (m, 4H, $2CH_2$-piperidine), 2.7 (s, 3H, CH_3), 3.0 (s, 3H, CH_3), MS: *m/z* (%) 346 (M^+, 100). The Anal: calc. for $C_{16}H_{18}N_4Se$ (345.3): C, 55.65; H, 5.21; N, 16.23. Found: C, 55.84; H, 5.34; N, 15.96%.

7,9-Dimethyl-4-morpholinopyrido[3',2':4,5]selenolo[3,2-d] pyrimidine (**16b**): White crystals (3.15 g, 91%), m.p. 166–168°C. ^1H NMR (DMSO-d_6): 9.8 (s, 1H, CH-pyrimidine), 7.8 (s, 1H, CH-pyridine), 4.3 (m, 4H, $2CH_2$-morpholine), 4.5 (m, 4H, $2CH_2$-morpholine), 3.1 (s, 3H, CH_3), 3.3 (s, 3H, CH_3). MS: *m/z* (%) 348 (M^+, 100%). Anal: calc. for $C_{15}H_{16}N_4OSe$ (347.3): C, 51.87; H, 4.61; N, 16.13. Found: C, 51.57; H, 4.68; N, 15.88%.

4-Hydrazino-7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-d]pyrimidine (**17**)
The chloro-compound **13** (2.96 g, 10 mmol) in ethanol (20 ml) was heated under reflux for 2 h with hydrazine hydrate (99%, 4 ml, 40 mmol). The product that formed while hot was collected and recrystallised from dioxan to give white crystals (2.60 g, 89%), m.p. >300°C. IR: ν_{max} 3100, 3300, 3400 cm^{-1} ($NHNH_2$). ^1H NMR (DMSO-d_6): δ 8.8 (s, 1H, NH), 8.3 (s, 1H, CH-pyrimidine), 7.1 (s, 1H, CH-pyridine), 4.9 (s, 2H, NH_2), 2.6 (s, 3H, CH_3), 2.9 (s, 3H, CH_3). MS: *m/z* (%) 292 (M^+-1). Anal: calc. for $C_{11}H_{11}N_5Se$ (292.2): C, 45.20; H, 3.76; N, 23.97. Found: C, 44.70; H, 3.50; N, 23.74%.

7,9-Dimethylpyrido[3',2':4,5]selenolo[2,3-e][1,2,4]triazolo[4,3-c] pyrimidine (**18**)
The hydrazine **17** (2.92 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 recrystallised from dioxan as white crystals (2.35 g, 78%), m.p. >300°C. ^1H NMR (TFA): δ 8.0 (s, 1H, CH-pyridine), 8.8 (s, 1H, CH-pyrimidine), 9.0 (s, 1H, CH-triazole) 3.0 (s, 3H, CH_3), 3.4 (s, 3H, CH_3). MS: *m/z* (%) 303 (M^+, 100). Anal: calc. for $C_{12}H_9N_5Se$ (302.2): C, 47.68; H, 2.98; N, 23.17. Found: C, 47.53; H, 3.05; N, 22.91%.

Ethyl 7,9-dimethylpyrido[3',2':4,5]selenolo[2,3-e][1,2,4]triazolo[4,3-c] pyrimidine-3-acetate (**19**)
The hydrazine **17** (2.92 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 recrystallised from ethanol as pale yellow crystals (2.91 g, 75%), m.p. 224–226°C. IR: ν_{max} 1730 cm^{-1} (C=O). ^1H NMR (TFA): δ 8.0 (s, 1H, CH-pyridine), 8.7 (s,1H, CH-pyrimidine), 4.6 (s, 2H, CH_2), 4.2 (m, 2H, CH_2-ester), 3.2 (s, 3H, CH_3), 3.6 (s, 3H, CH_3). 1.4 (t, 3H, CH_3-ester). MS: *m/z* (%) 389 (M^+, 41),387 (M^+, 19). Anal: calc. for $C_{16}H_{15}N_5O_2Se$ (388.3): C, 49.48; H, 3.86; N, 18.04. Found: C, 48.98; H, 3.55; N, 18.24%.

3,7,9-Trimethylpyrido[3',2':4,5]selenolo[2,3-e][1,2,4]triazolo[4,3-c] pyrimidine (**20**)
Compound **17** (2.92 g,10 mmol) in acetic anhydride (20 ml) was heated under reflux for 6 h. The precipitate that formed while hot was collected and recrystallised from dioxan: white crystals (2.52 g, 80%), m.p. >300°C. IR: ν_{max} 3050 cm^{-1} (CH-aromatic). ^1H NMR (TFA): δ 7.9 (s, 1H, CH-pyridine), 8.7 (s, 1H, CH-pyrimidine), 3.0 (s, 3H, CH_3), 3.2 (s, 3H, CH_3), 3.4 (s, 3H, CH_3-triazole). Anal: calc. for $C_{13}H_{11}N_5Se$ (316.2): C, 49.36; H, 3.48; N, 22.15. Found: C, 49.23; H, 3.67; N, 21.80%.

Ethyl N-(2-cyano-4,6-dimethylselenolo[2,3-b]pyridin-3-yl)methan-imidate (**21**)
The nitrile **2b** (2.5 g, 10 mmol) and triethyl orthoformate (7 ml) were refluxed in acetic anhydride (20 ml) for 5 h. The precipitate that formed on cooling was collected; recrystallisation from ethanol formed white crystals (2.88 g, 94%), m.p. 132–134°C. IR: ν_{max} 2200 cm^{-1} (CN). ^1H NMR (DMSO-d_6): 8.0 (s, 1H, N=CH), 7.0 (s, 1H, CH-pyridine), 4.2 (m, 2H, CH_2-ethoxy), 2.4 (s, 3H, CH_3-pyridine). 1.8 (s, 3H, CH_3-pyridine), 1.2 (t, 3H, CH_3-ethoxy), MS: *m/z* (%): 307 (M^+, 100). Anal: calc. for $C_{13}H_{13}N_3OSe$ (306.23): C, 50.98; H, 4.24; N, 13.72. Found: C, 50.57; H, 3.97; N, 13.83%.

3-Amino-3,4-dihydro-4-imino-7,9-dimethylpyrido[3',2':4,5]selenolo [3,2-d]pyrimidine (**22**)
The iminoether **21** (3.06 g, 10 mmol) was suspended in dioxan (10 ml), hydrazine hydrate (99%, 2 ml) was added, the reaction mixture was stirred at room temperature for 3 h. The solid product that formed was collected and recrystallised from dioxan as white crystals (2.54 g, 87%), m.p. >300°C. IR: ν_{max} 3100 (NH), 3300, 3400 cm^{-1} (NH_2). ^1H NMR (DMSO-d_6): δ 8.0 (s, 1H, CH-pyrimidine), 7.0 (s, 1H, CH-pyridine), 5.8 (s, 2H, NH_2), 2.7 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), MS: *m/z* (%) 292 (M^+-1, 93). Anal: calc. for $C_{11}H_{11}N_5Se$ (292.2): C, 45.20; H, 3.76; N, 23.97. Found: C, 45.31; H, 3.31; N, 24.28%.

7,9-Dimethylpyrido[3',2':4,5]selenolo[2,3-e][1,2,4]triazolo[1,5-c] pyrimidine (**23**)
The amino-imine **22** (2.92 g, 10 mmol) was heated under reflux for 4 h in triethyl orthoformate (10 ml). A solid product that separated while hot was collected and recrystallised from dioxan as white crystals (2.35 g, 78%), m.p. >300°C. IR: ν_{max} 3050 cm^{-1} (CH-aromatic). ^1H NMR (TFA): δ 8.0 (s, 1H, CH-pyridine), 8.8 (s, 1H, CH-pyrimidine), 9.0 (s, 1H, CH-triazole), 3.4 (s, 3H, CH_3), 3.0 (s, 3H, CH_3). MS: *m/z* (%) 303 (M^+, 100). Anal: calc. for $C_{12}H_9N_5Se$ (302.2): C, 47.68; H, 2.98; N, 23.17. Found: C, 47.53; H, 3.06; N, 23.42%.

Ethyl 7,9-dimethylpyrido[3',2':4,5]selenolo[2,3-e][1,2,4]triazolo[1,5-c] pyrimidine-2-acetate (**24**)
Compound **22** (2.92 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 recrystallised from ethanol as pale yellow crystals (2.91 g, 75%), m.p. 224–226°C. IR: ν_{max} 1730 cm^{-1} (C=O). ^1H NMR (TFA): δ 8.0 (s, 1H, CH-pyridine), 8.7 (s, 1H, CH-pyrimidine), 4.6 (s, 2H, CH_2), 4.2 (m, 2H, CH_2-ester), 3.2 (s, 3H, CH_3), 3.6 (s, 3H, CH_3), 1.4 (t, 3H, CH_3-ester). MS: *m/z* (%) 388 (16), 389 (M^+, 89), 390 (17). Anal: calc. for $C_{16}H_{15}N_5O_2Se$ (388.3): C, 49.48; H, 3.86; N, 18.04. Found: C, 49.39; H, 4.03; N, 17.83%.

2,7,9-Trimethylpyrido[3',2':4,5]selenolo[2,3-e][1,2,4]triazolo[1,5-c] pyrimidine (**25**)
Compound **22** (2.92 g,10 mmol) was heated under reflux for 6 h in acetic anhydride (20 ml). The precipitate that formed while hot was collected and recrystallised from dioxan as white crystals (2.52 g,

80%), m.p. >300°C. ^{1}H NMR (TFA): 7.9 (s, 1H, CH-pyridine), 8.7 (s, 1H, CH-pyrimidine), 3.0 (s, 3H, CH_3), 3.2 (s, 3H, CH_3), 3.4 (s, 3H, CH_3-triazole). MS: *m/z* (%) 317 (M^+, 22). Anal: calc. for $C_{13}H_{11}N_5Se$ (316.2): C, 49.36; H, 3.48; N, 22.15. Found: C, 49.12; H, 3.78; N, 22.06%.

Received 1 July 2007; accepted 5 October 2007
Paper 07/4722 doi: 10.3184/030823407X25506

References

1 D.E. Beattie, R. Crossley, A.C.W. Curran, G.T. Dixon, D.G. Hill, A.E. Lawrence and R.G. Shepherd, *J. Med. Chem.*, 1977, **20,** 714.
2 Tanabe Seiyaka Co., Ltd., Japan Patent 72 00 811, 1972; *Chem. Abstr*., 1972, **76**, 140 574.
3 H.S. Wood, in *Comprehensive organic chemistry*, Vol. 5. D.H.R. Barton and W.D. Ollis, eds, Pergamon, Oxford, 1979, p. 537.
4 G. Odhan and E. Stenhagen, *Acc. Chem. Res*., 1971, **4,** 121.
5 T. Maier, S. Scheiblich and H.S. Baltruschat, US Pat., 11 064 (2001); *Chem. Abstr*., 2001, **135**, 133 440w.
6 S.A. Armstrong, J.M. Berge, P. Brown, J.S. Elder, A.K. Forrest, O.W. Hamprecht and R.L. Jarrest, PCT Int. Appl. 1999, WO 0071 524; *Chem. Abstr*., 2001, **134**, 17 496.
7 Proctor and Gamble Ltd., US Pat. 3 236 733 (1966); *Chem. Abstr*., 1966, **64,** 17 364.
8 A. Rasching, US Pat. 2 937 118 (1960); *Chem. Abstr*., 1966, **54**, 17 807.
9 A.V. Gasparian, Y.J. Yao, J. Liu, A.Y. Yemelyanov, L.A. Lyakh, J.T. Slaga and I.V. Budunova, *Molec. Cancer Therapeut*, 2002, **1**, 1079.
10 J. Fleming, A. Ghose and P.R. Harrison, *Nutrition Cancer*, 2001, **40,** 42.
11 A. Ghose, J. Fleming, K. El-Bayoumy and P.R. Harrison, *Cancer Res*., 2001, **61,** 7479.
12 W. Wu, K. Murakami, M. Koketsu, Y. Yamada and I. Saiki, *Anticancer Res.*, 1999, **19,** 5375.
13 C. Hu, P. Zhang, H. Li, Z. Ji and B. Liu, *Huaxue Tongbao*, 2002, **65,** 162; *Chem. Abstr*., 2002, **137**, 169 434.
14 M. Koketsu, K. Tanaka, Y. Takenaka, C.D. Kwong and H. Ishihara, *Eur. J. Pharm. Sci*., 2002, **15,** 307.
15 G. Mugesh, W.W. DuMont and H. Sies, *Chem. Rev.*, 2001, **101,** 2125.
16 E.V. Ratushnaya, Y.I. Kirova, M.A. Suchkov, B.I. Drevko and V.B. Borodulin, *J. Chem. Pharm.,* 2002, **36**, 652.
17 C. Jacob, G. Giles and F. Fry, US Pat. (2004) WO2004 047 925.
18 Sh.H. Abdel-Hafez, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 2563.
19 Sh.H. Abdel-Hafez, *Russian J. Org. Chem*., 2005, **41**, 396.
20 Sh.H. Abdel-Hafez, H.W. Anthosen, H.R. Sliwka and V. Partali, *Phosphorus, Sulfur, Silicon*, 2005, **180**, 2217.
21 M.A. Abbady, Sh.H. Abdel-Hafez, M.M. Kandeel and M.I. Abdel-Monem, *Molecules,* 2003, **8,** 622.
22 M.A. Abbady and Sh.H. Abdel-Hafez, *Phosphorus, Sulfur, Silicon*, 2000, **160,** 121.
23 Sh.H. Abdel-Hafez, Sh.A. Abdel-Mohsen and Y.A. El-Ossaily, *Phosphorus, Sulfur, Silicon*, 2006, **181**, 2297.
24 Kh.M. Hassan, R.A. Ahmed, Sh.H. Abdel-Hafez and M.A. Abdel-Azim, *Phosphorus, Sulfur, Silicon*, 2006, **181,** 481.
25 V.P. Litvinov, V. Yu. Mortikov, Yu.A. Sharanin and A.M. Shestopalov, *Synthesis,* 1985, **1**, 98.