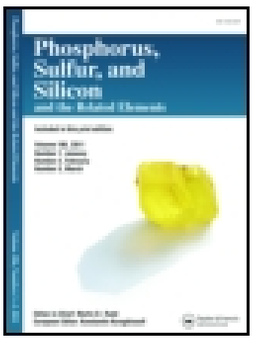

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Synthesis of some new pyrazolobenzothienopyrimidineselanyl derivatives

Refaah A. Alshahrani,[a] Adel A. Gobouri,[a] Naif A. Alshanbari,[a] Saleh A. Ahmed,[b] and Shams H. Abdel-Hafez.[a,c] [1]

a Department of Chemistry, Faculty of Science, Taif University, Taif KSA;

b Department of Chemistry, Faculty of Science, Umm Al-Qura University, Makkah KSA;

c Department of Chemistry, Faculty of Science, Assiut University, Assiut Egypt.

Abstract – The targeted synthesis of 2-(methylsulfanyl)-6-(furan-2-yl)-4(3*H*)-selenoxo -pyrimidine-5-carbonitrile failed due to the formation 1-methyl-2-methylsulfanyl-6-oxo -4-(furan-2-yl)-1,6-dihydropyrimidine-5-carbonitrile. A new series of 5,6,7,8-tetrahydro-1-benzo thieno[2,3-d]pyrimidine-4-yl substituted selanyl derivatives were prepared by the reaction of sodium diselenide with 4-chloro-5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidine followed by the reaction with chloroacetic acid derivatives such as ethyl chloroacetate, chloroacetamide or chloroacetonitrile. Hydrazinolysis of ethyl (5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidine-4-ylselanyl)acetate with hydrazine hydrate gave the corresponding hydrazino derivative. The latter reacted with ethyl acetoacetate, acetylacetone, diethyl malonate, ethoxymethylenemalononitrile or ethyl 2-cyano-3-ethoxyacetate to afford 5-methyl-2-[2-(5,6,7,8-tetrahydro-1-benzothieno [2,3-d]pyrimidine-4-ylselanyl)acetyl]-2,4-dihydropyrazol-3-one, 1-(3,5-dimethylpyrazol-1-yl)-2- (5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-4-ylselanyl)ethanone, 1-[2-(5,6,7,8-tetrahydro -1-benzothieno[2,3-d]pyrimidine-4-

[1] Contact: Shams H. Abdel-Hafez: shams@aun.edu.eg; shams_abdelhafez@yahoo.com
Chemistry Department, Faculty of Science, Taif University, Taif 21974, Saudi Arabia;
Department of Chemistry, Faculty of Science, Assiut University, Assiut, Egypt

ylselanyl)acetyl]-2,4-dihydropyrazolidine-3,5-dione and 5-Amino-1-[2-(5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-4-ylselanyl)acetyl]-1*H*-pyrazol -4-yl substituted carbonitrile or ethyl carboxylate, respectively. The structure of the novel compounds was confirmed by spectroscopic tools (IR, ^{1}H NMR ^{13}C NMR and mass spectra) and elemental analysis.

Keywords: Benzothienopyrimidine diselenide; benzothienopyrimidine selanyl derivatives; pyrazolbenzothienopyrimidine selanyl derivatives

INTRODUCTION

Pyrimidine derivatives play a vital role in many biological activities, e. g. in several vitamins and purines such as uracil, thymine, and cytosine.[1] According to the literature, pyrimidine derivatives exhibit various pharmacological activities as antibacterial,[2] antifungal,[3] antiviral,[4,5] anticancer,[6,7] analgesic and anti-inflammatory drugs.[8] In addition, thienopyrimidine derivatives show many biological activities, such as anticancer,[9] antiviral,[10] antitumor,[11] anti-inflammatory,[12] antimicrobial,[13] and antimalarial,[14]. Despite the high toxicity of many selenium compounds, they show anti-viral, anti-microbial, anti-tumor[15,16] and anti-cancer[17,18] activity.[19-27] Organoselenium compounds have been tested as agents against bacteria, viruses, fungi, parasites, as antihistamines, as well as anti-cancer drugs.[28-35] Therefore, we decided to expand our investigations to introduce selenium into pyrimidine derivatives, hoping to obtain a new series of heterocyclic systems with the anticipated biological and pharmaceutical effects.

RESULTS and DISCUSSION

To attain our target, the introduction of selenium into the pyrimidine ring, we started from chlorobenzothienopyrimidine **6** which was prepared according to known methods.[36, 37] The reaction of cyclohexanone (**1**), elemental sulfur (**2**) and ethyl cyanoacetate (**3**) gave ethyl 2-aminobenzothiophene-3-carboxylate **4**. Refluxing of **4** with formamide led to the benzothienopyrimidinone derivative **5,** the reaction of which with a mixture of $POCl_3$/ PCl_5 gave 4-chloro-1-benzothieno[2,3-d]pyrimidine **6**. The structure of **6** was confirmed by its ^1H and ^{13}C NMR spectra and elemental analysis. The synthesis of the target compound 4,4'-bis(5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidine) diselenide (**7**) was achieved by the reaction of **6** with sodium diselenide in ethanol/DMF (**Scheme 1**). The structure of **7** was established by elemental analysis, ^1H NMR, ^{13}C NMR, IR and mass spectra. The IR spectrum showed absorptions at 1585 (C=N) cm^{-1}. The ^1H NMR data showed the characteristics signals at δ = 1.76-3.39 (tetrahydrobenzene) and 9.08 (CH-pyrimidine). In addition, the elemental analysis, revealed the disappearance of the chloro substituent.

Reactions of **7** with different chloroacetyl derivates such as ethyl chloroacetate, chloroacetamide or chloroacetonitrile afforded the corresponding selanyl derivatives **8**-**10**. The IR spectra showed the characteristic peaks at 1700 (C=O) for **8**, 1670 (C=O) for **9** and 2217 (CN) cm^{-1} for **10**. The ^1H NMR spectra showed a triplet for the methyl group and quartet peaks for the methylene group of **8**, and the characteristic peaks at 6.56 (NH_2-group), 2.71 (CH_2-group) for **9** and 2.51 (CH_2-group) for **10** (**Scheme 2**).

Hydrazinolysis of ethyl (5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidine-4-ylselanyl)acetate

(**8**) with hydrazine hydrate gave (5,6,7,8-Tetrahydro-1-benzothieno[2,3-d]pyrimidine-4-ylselanyl) acetohydrazide (**11**). Spectroscopic tools and elemental analysis confirmed the structure of the hydrazide **11**. The broad utility of heterocyclic hydrazine as precursors for the synthesis of several condensed systems containing pyrazole derivatives (**12-15a,b**) has received increasing attention. It was of interest to examine the chemistry and reactivity of the hydrazide **11** as a key intermediate. Condensation of **11** with ethyl acetoacetate and acetyl acetone in the presence of sodium ethoxide under ring closure gave the cyclization products 5-methyl-2-[2-(5,6,7,8-tetrahydro-1-benzothieno [2,3-d]pyrimidine-4-ylselanyl)acetyl]-2,4-dihydro-pyrazol-3-one **12** and 1-(3,5-dimethyl-pyrazol -1-yl)-2-(5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-4-ylselanyl)ethanone **13**. Reactions of **11** with diethyl malonate and ethoxymethylenemalononitrile or ethyl 2-cyano-3-ethoxyacetate gave the corresponding 1-[2-(5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidine-4-ylselanyl)acetyl]-4,5-dihydropyrazolidine-3,5-dione (**14**) and 5-amino-1-[2-(5,6,7,8-tetrahydro-1-benzothieno[2,3-d] pyrimidin-4-ylselanyl)acetyl]-1*H*-pyrazol-4-substituted (**15a,b**) respectively. (**Scheme 3**).
The structure of these compounds (**12-15a,b**) was confirmed by elemental analyses, IR, ^{1}H NMR and ^{13}C NMR spectra. The data of all new compounds data are given in the **Experimental**.

CONCLUSION

Pyrazolobenzothienopyrimidine selanyl derivatives were synthesized. They represent a new series of selenium containing heterocycles. The novel compounds are 5-methyl-2-[2-(5,6,7,8 -tetrahydro-1-benzothieno[2,3-d]pyrimidine-4-ylselanyl)acetyl]-2,4-dihydropyrazol-3-one, 1-(3,5-dimethylpyrazol-1-yl)-2-(5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-4-ylselanyl)ethanone,

1-[2-(5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidine-4-ylselanyl)acetyl]-2,4-dihydropyrazol idine-3,5-dione and 4-substituted 5-amino-1-[2-(5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin -4-ylselanyl)acetyl]-1*H*-pyrazolcarbonitrile or -carboxylic acid ethyl ester.

EXPERIMENTAL

Melting points (uncorrected) were determined by using the Kofler melting point apparatus. IR spectra (KBr, cm^{-1}) were recorded on a Pye–Unicam SP3-100 instrument at King Abdel-Aziz University. ^{1}H NMR spectra (400 MHz) were obtained on a Varian EM 390 USA instrument at King Abdel-Aziz University. ^{13}C NMR spectra (100 MHz) were recorded on a JNM-LA spectrometer at King Abdel-Aziz University, Saudi Arabia. DMSO-d_6 or $CDCl_3$ were used as solvents for both ^{1}H and ^{13}C-NMR spectroscopy. The spectra were internally referenced to TMS. Peaks are reported in ppm downfield of TMS. Multiplicities are reported as singlet (s), doublet (d), triplet (t) quartet (q). Mass spectra were recorded on a JEOL-JMS-AX 500 at Cairo national research center, Cairo, Egypt. Elemental analyses were obtained on an Elementar Vario EL 1150 oC analyzer (Heraeus, Germany, Cairo University). Elemental analyses have been used to determine the purity (> 95%) of the described compounds. Thin layer chromatography (TLC) using silica gel plates checked the purity of the compounds. Column chromatography was carried out on 0.04-0.063 mm (Merck) silica gel, TLC was carried out on aluminum backed silica plates by Merck and plates were revealed using a UV 254 light.

Compounds **4** and **5** were prepared as previously described.[38]

4-Chloro-5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidine (**6**).

A mixture of **5** (2. 06 g. 0.01 mol) was refluxed with PCl_5 (2.51 g, 0. 012 mol) and $POCl_3$ (5 mL)

for 3h. After cooling, the mixture was carefully poured into over ice and ammonia solution in small portions. The solid product was filtered off and recrystallized from benzene to give **6** as pale brown crystals. Yield 75 %. Mp. 115-117 °C. IR:1600 (C=N). ^{1}H NMR ($CDCl_3$), δ: 1.94-3.11 (m, 8H, tetrahydrobenzene), 8.73 (s, 1H, CH-pyrimidine). ^{13}C NMR ($CDCl_3$), δ: 168.8, 153.2, 151.4, 139.6, 128.8, 127.2, 121.5, 26.0, 23.5, 22.5. MS *m/z* (%): 224 [M^+, 25%]. Anal. Calcd. for $C_{10}H_9ClN_2S$ (224.71): C, 53.45; H, 4.04; Cl, 15.78; N, 12.47; S, 14.27 %. Found C, 53.55; H, 4.00; Cl, 15.45; N, 12.22; S, 14.11.

4,4'-Bis(5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidine)diselenide (**7**)

A mixture of **6** (2.24 g, 0.01 mol), selenium metal powder (0.79 g, 0.01 mol) and $NaBH_4$ (0.74 g, 0.02 mol) in EtOH (30 mL) was stirred until colorless in an ice bath. After that, DMF (20 mL) was added. The mixture became deep red brown and an additional amount of elemental selenium (0.79 g, 0.01 mol) was added with ethanol (5 mL). The reaction mixture was refluxed for 3 h, then cooled and poured into ice/HCl (200 g). The solid was filtered, dried and recrystallized from ethanol. Yield 75%. Mp. 232-234 °C. IR: 1585 (C=N). ^{1}H NMR ($CDCl_3$), δ: 1.76-3.39 (m, 8H, tetrahydrobenzene), 9.08 (s, 1H, CH-pyrimidine). ^{13}C NMR ($CDCl_3$), δ: 174.5, 166.9, 153.1, 148.5, 138.2, 133.7, 128.4, 24.5, 21.1, 17.1. MS, *m/z* (%): 535 [M^+–1, 5%]. Anal. Calcd. for $C_{20}H_{18}N_4S_2Se_2$ (536.43): C, 44.78; H, 3.38; N, 10.44; S, 11.95 %. Found C, 44.54; H, 3.35; N, 10.27; S, 11.88.

5,6,7,8-Tetrahydro-1-benzothieno[2,3-d]pyrimidine-4-ylselanyl) derivatives **8**,**9** and **10**

General procedures:

A small portion of $NaBH_4$ was added to **7** (0.01 mol) in EtOH (20 mL). The reaction mixture was stirred at room temperature until it was colorless. Then, ethyl chloroacetate, chloroacetamide

or chloroacetonitrile (0.01 mol) was added. The reaction mixture was refluxed for 2 h and after that poured onto crushed ice (200 g). Then, the solution was acidified with acetic acid. The precipitated solid was filtered off and dried.

Ethyl (5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidine-4-ylselanyl)acetate (**8**);

Yield 65%. Mp. 220-222 °C. IR: 1700 (C=O), 1585 (C=N). ^{1}H NMR ($CDCl_3$), δ: 1.05-1.29 (t, 3H, CH_2-$\underline{CH_3}$), 1.76-3.39 (m, 8H, tetrahydrobenzene), 3.1 (s, 2H, CH_2), 4.13 (q, 2H, $\underline{CH_2}$-CH_3), 9.08 (s, 1H, CH-pyrimidine). ^{13}C NMR ($CDCl_3$), δ: 174.5, 171.1, 166.9, 153.1, 148.5, 138.2, 133.7, 128.4, 65.4, 27.5, 24.5, 21.1, 17.1, 14.5. MS, *m/z* (%): 355 [M+, 10%]. Anal. Calcd. for $C_{14}H_{16}N_2O_2SSe$ (355.31): C, 47.32; H, 4.54; N, 7.88; S, 9.02 %. Found C, 47.14; H, 4.25; N, 7.77; S, 8.87.

(5,6,7,8-Tetrahydro-1-benzothieno[2,3-d]pyrimidine-4-ylselanyl)acetamide (**9**);

Yield 70%. Mp. 230-232 °C. IR: 1670 (C=O), 1585 (C=N). ^{1}H NMR ($CDCl_3$), δ: 6.56 (s, 2H, NH_2), 1.75-3.35 (m, 8H, tetrahydrobenzene), 2.71 (s, 2H, CH_2), 9.08 (s, 1H, CH-pyrimidine). ^{13}C NMR ($CDCl_3$), δ: 174.5, 171.1, 166.9, 153.1, 148.5, 138.2, 133.7, 128.4, 30.5, 24.5, 21.1, 17.1. MS, *m/z* (%): 326 [M^+, 5%]. Anal. Calcd. for $C_{12}H_{13}N_3OSSe$ (326.28): C, 44.17; H, 4.02; N, 12.88; S, 9.83 %. Found C, 44.10; H, 3.99; N, 12.57; S, 9.47.

(5,6,7,8-Tetrahydro-1-benzothieno[2,3-d]pyrimidine-4-ylselanyl)carbonitrile (**10**);

Yield 75%. Mp. 224-226 °C. IR: 2217 (CN), 1600 (C=N). ^{1}H NMR ($CDCl_3$), δ: 1.75-3.35 (m, 8H, tetrahydrobenzene), 2.51 (s, 2H, CH_2), 9.50 (s, 1H, CH-pyrimidine). ^{13}C NMR ($CDCl_3$), δ: 166.9, 153.1, 148.5, 138.2, 133.7, 128.4, 115.5, 12.5, 24.5, 21.1, 17.1. MS, *m/z* (%): 308 [M^+, 15%]. Anal. Calcd. for $C_{12}H_{11}N_3SSe$ (308.26): C, 46.76; H, 3.60; N, 13.63; S, 10.40 %. Found C, 46.70; H, 3.29; N, 13.50; S, 10.27.

(5,6,7,8-Tetrahydro-1-benzothieno[2,3-d]pyrimidine-4-ylselanyl)acetohydrazide (**11**).

Compound **15** (3.55 g, 0.01 mol) was stirred in dioxan (10 mL) at room temperature. After that, hydrazine hydrate (80%) (15 mL) was added. The reaction mixture was refluxed for 12 h. The reaction mixture was poured onto crushed ice (100 g), the solid was filtered off, dried and recrystallized from EtOH. Yield 75%. Mp. 242-244 °C. IR: 1660 (C=O), 3400, 3300, 3150 $NHNH_2$), 1600 (C=N). ^{1}H NMR ($CDCl_3$), δ: 6.50 (s, 2H, NH_2), 1.75-3.35 (m, 8H, tetrahydrobenzene), 2.71 (s, 2H, CH_2), 12.02 (s, 1H, NH), 9.20 (s, 1H, CH-pyrimidine). ^{13}C NMR ($CDCl_3$), δ: 174.5, 170.5, 171.1, 166.9, 153.1, 148.5, 138.2, 133.7, 128.4, 29.5, 24.5, 21.1. MS, *m/z* (%): 342 [M^++1, 7%]. Anal. Calcd. for $C_{12}H_{14}N_4OSSe$ (341.29): C, 42.23; H, 4.13; N, 16.42; S, 9.40 %. Found C, 42.10; H, 3.95; N, 16.27; S, 9.27.

5-Methyl-2-[2-(5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidine-4-ylselanyl)acetyl)-2,4-dihydro-pyrazol-3-one (**12**)

Compound **11** (3.41 g, 0.01 mol) was dissolved in ethanol (10 mL). Ethyl acetoacetate (1 mL) and a few drops of NaOEt in EtOH were added. The reaction mixture was refluxed for 5 h. After cooling, the reaction mixture was poured onto crushed ice (100 g), the solid was filtered off, dried and recrystallized from ethanol; Yield 50%. Mp. 248-250 °C. IR: 1660 (C=O), 1670 (C=O), 1600 (C=N). ^{1}H NMR ($CDCl_3$), δ: 1.75-3.35 (m, 8H, tetrahydrobenzene), 2.45, 2.71 (s, 4H, $2CH_2$), 2.49 (s, 3H, CH_3). 9.50 (s, 1H, CH-pyrimidine). ^{13}C NMR ($CDCl_3$), δ: 174.5, 171.1, 166.9, 152.6, 153.1, 148.5, 141.1, 138.2, 133.7, 110.9, 128.4, 30.5, 24.5, 21.1, 13.5, 14.0. MS, *m/z* (%): 407 [M^+, 5%]. Anal. Calcd. for $C_{16}H_{16}N_4O_2SSe$ (407.35): C, 47.18; H, 3.96; N, 13.75; S, 7.87 %. Found C, 47.00; H, 3.59; N, 13.50; S, 7.49.

1-(3,5-Dimethyl-pyrazol-1-yl)-2-(5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-4-ylselanyl)

ethanone (**13**).

Compound **11** (3.41 g, 0.01 mol) was dissolved in ethanol (10 mL). Acetylacetone (1 mL) and NaOEt was added drop wise. The reaction mixture was refluxed for 5 h. The mixture was poured onto crushed ice (100 g). The solid was filtered off, dried and recrystallized from ethanol; Yield 45%. Mp. 250-252 °C. IR: 1670 (C=O), 1610 (C=N). ^{1}H NMR ($CDCl_3$), δ: 7.38 (s, 1H, CH-pyrazol), 1.75-3.35 (m, 8H, tetrahydrobenzene), 2.71 (s, 2H, CH_2), 2.54-2.48 (m, 6H, $2CH_3$). 9.50 (s, 1H, CH-pyrimidine). ^{13}C NMR ($CDCl_3$), δ: 174.5, 171.1, 166.9, 153.1, 152.6, 148.5, 141.1, 138.2, 133.7, 110.9, 128.4, 32.5, 30.5, 24.5, 21.1, 13.5, 14.0. MS, *m/z* (%): 405 [M^+, 10%]. Anal. Calcd. for $C_{17}H_{18}N_4OSSe$ (405.38): C, 50.37; H, 4.48; N, 13.82; S, 7.91 %. Found C, 50.17; H, 4.39; N, 13.58; S, 7.69.

1-[2-(5,6,7,8-Tetrahydro-1-benzothieno[2,3-d]pyrimidine-4-ylselanyl)acetyl]-4,5-dihydro-pyrazol idine-3,5-dione (**14**)

Compound **11** (3.41 g, 0.01 mol) and diethyl malonate (1.52 mL) in AcOH (50 mL) were refluxed for 5 h. After cooling, the reaction mixture was poured onto crushed ice (100 g). The solid was filtered off, dried and recrystallized from EtOH; Yield 55%. Mp. 240-242 °C. IR: 3150 (NH), 1660 (C=O), 1665 (C=O), 1670 (C=O), 1600 (C=N). ^{1}H NMR ($CDCl_3$), δ: 1.75-3.35 (m, 8H, tetrahydrobenzene), 2.40, 3.70 (s, 4H, $2CH_2$), 8.10 (s, 1H, NH), 9.50 (s, 1H, CH-pyrimidine). ^{13}C NMR ($CDCl_3$), δ: 172.5, 171.1, 168.1, 166.9, 152.6, 153.1, 148.5, 141.1, 138.2, 133.7, 128.4, 110.9, 46.5, 27.8. MS, *m/z* (%): 409 [M^+, 8%]. Anal. Calcd. for $C_{15}H_{14}N_4O_3SSe$ (409.32): C, 44.01; H, 3.45; N, 13.69; S, 7.83 %. Found C, 43.95; H, 3.39; N, 13.55; S, 7.69.

4-Substituted 5-amino-1-[2-(5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-4-ylselanyl)acetyl] -1H-pyrazolcarbonitrile or carboxylic acid ethyl ester (**15a,b**).

General procedures

Compound **11** (3.41 g, 0.01 mol) in AcOH (50 mL) and ethoxymethylenemalononitrile or ethyl 2-cyano-3-ethoxyacetate (0.01 mol) were refluxed for 3 h. The reaction mixture was poured onto crushed ice (100 g), the solid was filtered off, dried and recrystallized from EtOH.

15a; Yield 42%. Mp. 260-262 °C. IR: 3350, 3150 (NH_2), 2217(CN) 1670 (C=O). ^{1}H NMR ($CDCl_3$), δ: 7.38 (s, 1H, CH-pyrazol), 6.50 (s, 2H, NH_2) 1.75-3.35 (m, 8H, tetrahydrobenzene), 2.70 (s, 2H, CH_2), 9.50 (s, 1H, CH-pyrimidine). ^{13}C NMR ($CDCl_3$), δ: 174.5, 171.1, 166.9, 153.1, 152.6, 148.5, 141.1, 138.2, 133.7, 110.9, 128.4, 30.5, 24.5, 32.5, 21.1, 13.5. MS, *m/z* (%): 417 [M^+, 10 %]. Anal. Calcd. for $C_{16}H_{14}N_6OSSe$ (417.35): C, 46.05; H, 3.83; N, 20.14; S, 7.68 %. Found C, 45.88; H, 3.79; N, 20.00; S, 7.60.

15b; Yield 45%. Mp. 200-202 °C. IR: 3350, 3150 (NH_2), 1700 (C=O), 1670 (C=O). ^{1}H NMR ($CDCl_3$), δ: 7.88 (s, 1H, CH-pyrazol), 1.75-3.45 (m, 8H, tetrahydrobenzene), 2.70 (s, 2H, CH_2), 4.30 (q, 2H, CH_2), 6.50 (s, 2H, NH_2), 1.79 (t, 3H, CH_3). 9.50 (s, 1H, CH-pyrimidine). ^{13}C NMR ($CDCl_3$), δ: 174.5, 171.1, 166.9, 153.1, 152.6, 148.5, 141.1, 138.2, 133.7, 110.9, 106.1, 128.4, 61.5, 32.5, 30.5, 24.5, 23.1, 14.0. MS m/z (%): 464 [M^+, 8%]. Anal. Calcd. for $C_{18}H_{19}N_5O_3SSe$ (464.40): C, 46.55; H, 4.12; N, 15.08; S, 6.90 %. Found C, 46.37; H, 4.00; N, 15.00; S, 6.79.

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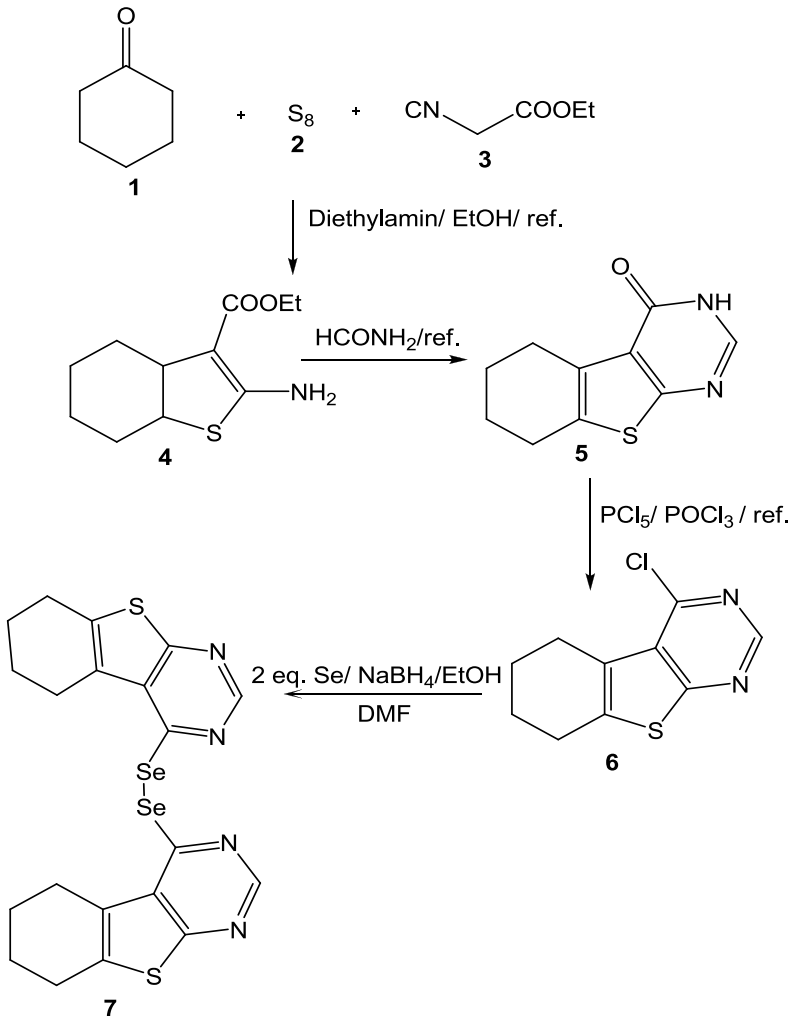
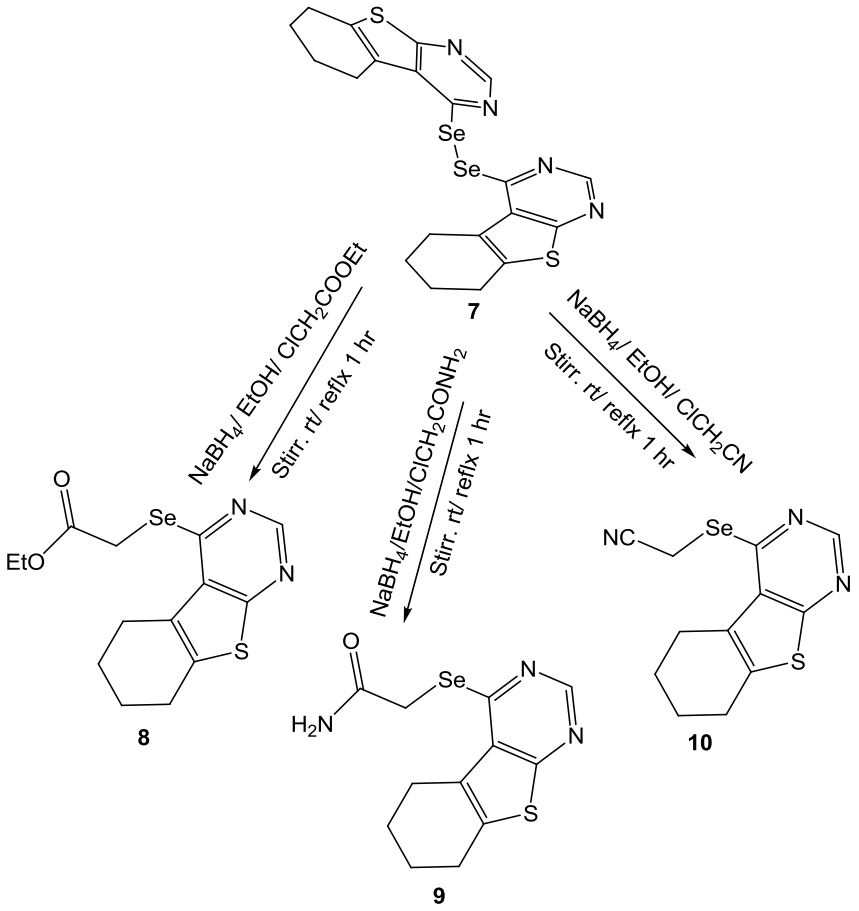
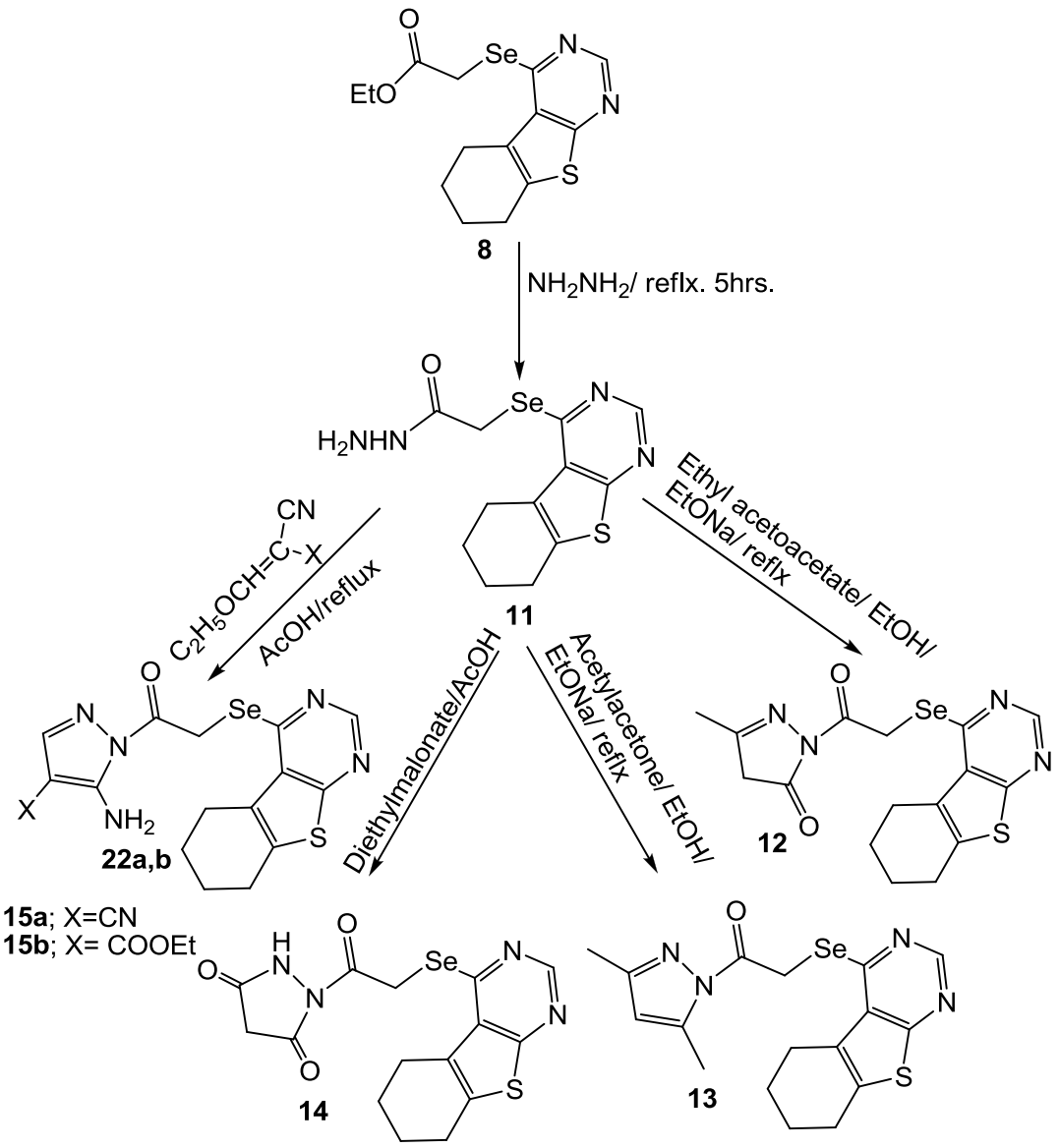


Scheme 1. Synthesis of 4,4'-bis(5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidine) diselenide **7**



Scheme 2. Synthesis of benzothienopyrimidine selanyl derivatives



Scheme 3. Synthesis of pyrazolbenzothienopyrimidine selanyl derivatives