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Selenium-Containing Heterocycles. Synthesis and Reactions of 2-Amino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carbonitrile with Anticipated Biological Activity*,**

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Abstract—Reaction of 2-amino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carbonitrile with ethylenediamine in the presence of a catalytic amount of carbon disulfide afforded 2-amino-3-(4,5-dihydro-1*H*-imidazol-2-yl)-4,5,6,7-tetrahydro-1-benzoselenophene. Cyclocondensation of the latter with triethyl orthoformate, benzaldehyde, and carbon disulfide gave tetracyclic imidazobenzoselenophenopyrimidine derivatives. Treatment of 2,3,5,6,8,9,10,11-octahydroimidazo[2,1-*c*][1]benzoselenopheno[3,2-*e*]pyrimidine-5-thione with hydrazine hydrate led to the corresponding 5-hydrazino derivative whose reactions with triethyl orthoformate and sodium nitrite were accompanied by closure of 1,2,4-triazole and tetrazole rings, respectively. Fused benzoselenophenopyrimidine systems were also obtained by reaction of 2-amino-4,5,6,7-tetrahydrobenzo-1-selenophene-3-carbonitrile with formamide, carbon disulfide, and phenyl isothiocyanate. Some newly synthesized compounds were tested for antimicrobial and antifungal activity.

In the recent years, interest in the chemistry of selenium-containing compounds has increased remarkably due to their chemical properties [1–5], biological activity, and pharmaceutical potential [6–10]. Some organoselenium compounds are known as effective insecticides, microbicides [11], prooxidants [12], and antimycobacterial agents [13]. With the goal of using less toxic selenium compounds for the synthesis of selenium-containing heterocycles, we prepared 2-amino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carbonitrile (**I**) from cyclohexylidenemalonodinitrile and metallic selenium [14]. In continuation of our studies on the preparation of novel heterocyclic systems containing sulfur and selenium atoms [15–17], the present communication describes the synthesis of new selenium-containing heterocycles on the basis of benzoselenophene derivative **I**.

2-Amino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carbonitrile (**I**) was prepared according to the procedure reported in [14] with some modifications: metallic selenium was added to cyclohexylidenemalonodinitrile in ethanol in the presence of triethylamine as catalyst. Compound **I** was brought into reaction with ethylenediamine in the presence of carbon disulfide to obtain 2-amino-3-(4,5-dihydro-1*H*-imidazol-2-yl)-4,5,6,7-tetrahydro-1-benzoselenophene (**II**) and 2,3,5,6,8,9,10,11-octahydroimidazo[2,1-*c*][1]benzoselenopheno[3,2-*e*]pyrimidine-5-thione (**IV**) as by-product (Scheme 1). Compound **II** was subjected to heterocyclization to tetracyclic imidazobenzoselenophenopyrimidine systems in different ways. Treatment of **II** with triethyl orthoformate gave 2,3,8,9,10,11-hexahydroimidazo[2,1-*c*][1]benzoselenopheno[3,2-*e*]-pyrimidine (**III**). The reaction of **II** with benzaldehyde under conditions analogous to those reported in [18], led to formation of 5-phenyl-2,3,5,6,8,9,10,11-octahydroimidazo[2,1-*c*][1]benzoselenopheno[3,2-*e*]pyrimidine (**V**). Thione **IV** was also obtained by heating compound **II** with carbon disulfide in boiling dry pyridine. The same product was also formed together with **II** directly from nitrile **I**, ethylenediamine, and excess carbon disulfide at 60°C (reaction time 48 h); it can be isolated by fractional crystallization from ethanol. Samples of **IV** prepared by the two methods were identical in chemical and physical properties.

Pyrimidinethione **IV** was readily converted into the corresponding 5-hydrazino derivative **VI** by treatment with hydrazine hydrate. Heterocyclization of **VI** by the action of triethyl orthoformate or sodium nitrite in

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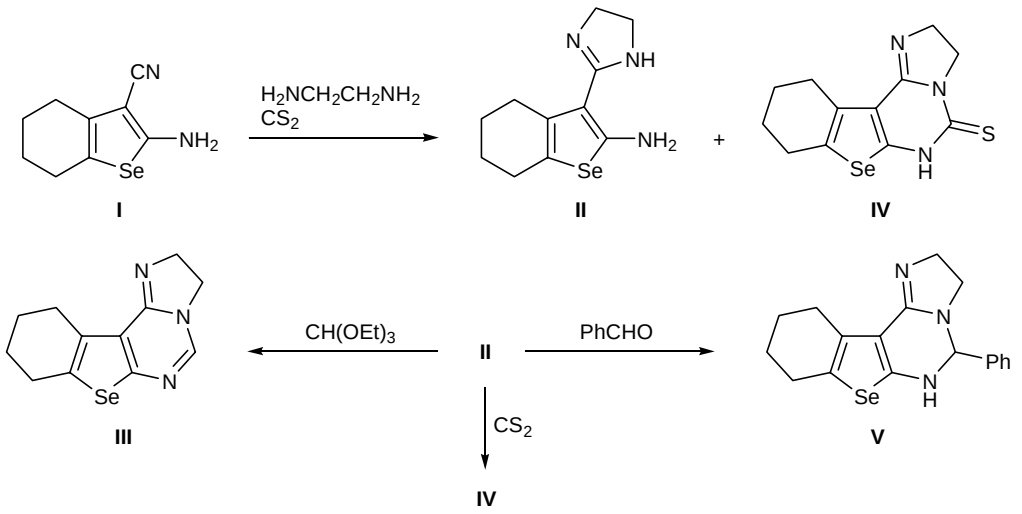
Scheme 1.



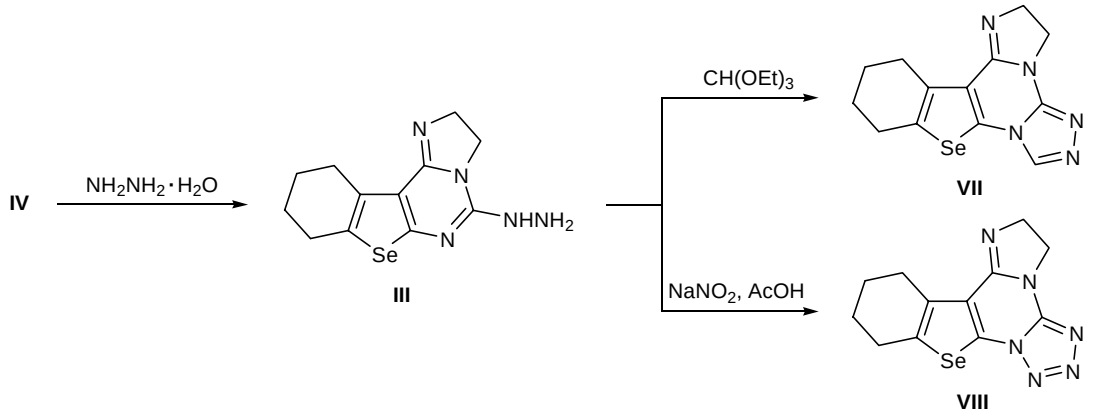
acetic acid gave fused 1,2,4-triazole and tetrazole derivatives (compounds **VII** and **VIII**, respectively; Scheme 2).

The reaction of compound **I** with formamide afforded 4-amino-5,6,7,8-tetrahydro[1]benzoselenopheno[2,3-*d*]pyrimidine (**IX**). Ethoxymethyleneimino derivative **X** was obtained by treatment of **I** with triethyl orthoformate in acetic anhydride. By reactions of amino nitrile **I** with carbon disulfide and phenyl isothiocyanate in pyridine, octahydrobenzoselenopheno-[2,3-*d*]pyrimidine derivatives **XI** and **XII**, respectively, were prepared (Scheme 3).

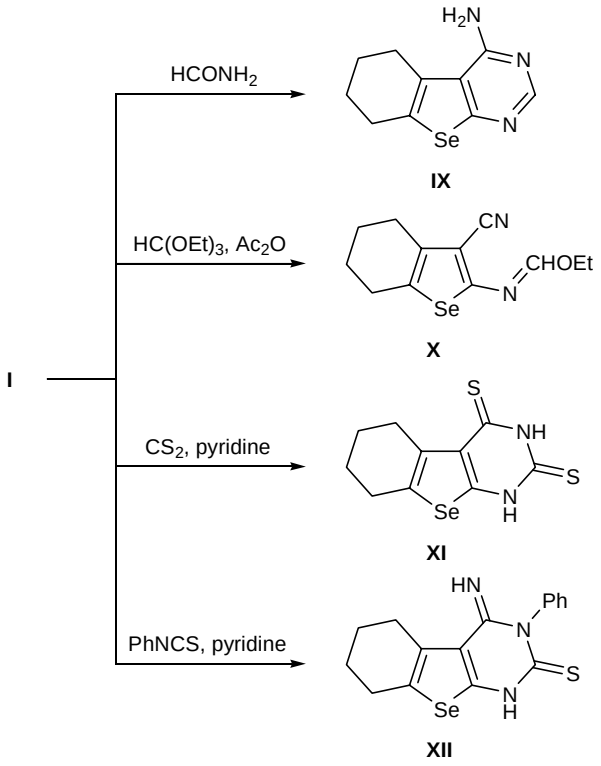
However, the product obtained by heating compound **I** in boiling acetic anhydride was identified as 2-acetylamino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carbonitrile (**XIII**), while the expected benzoselenophenopyrimidine derivative (**XIV**) was not detected. Diazotization of **I** with sodium nitrite in acetic acid led to formation of 4-chloro-5,6,7,8-tetrahydro[1]benzoselenopheno[2,3-*d*][1,2,3]triazine (**XV**), in keeping with the data of [19] (Scheme 4).

Some newly synthesized compounds were tested for antibacterial activity against *Bacillus cereus* and *Staphylococcus aureus* and for antifungal activity against *Candida albicans*, *Tricophyton rubrum*, and *Chrysosporium tropicum*. Chloramphenicol (5%) and Terbinafine (5%) were used as standards, respectively. The compounds were tested by the disc-diffusion technique [20, 21]. Samples were dissolved in dimethyl sulfoxide to a concentration *c* of 5%, and filter paper discs (Whatman no. 3, 5 mm in diameter) were impregnated with the solutions. The discs were placed on the surface of solidified Nutrient agar dishes seeded by the test bacteria or Czapek's Dox agar dishes seeded by the test fungi. The inhibition zones were measured in millimeters by the end of incubation period (48 h at 37°C for bacteria and 28°C for fingi). The results are collected in table. As follows from these data, among

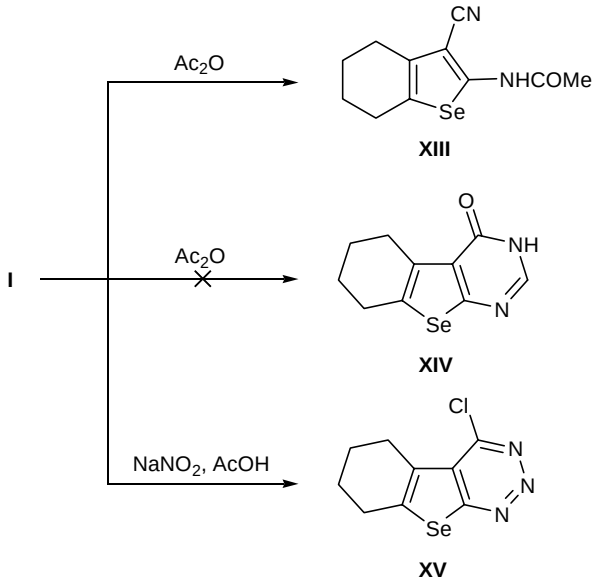
Scheme 2.



Scheme 3.



Scheme 4.



compounds **I**, **IX**, **X**, **XII**, **XIII**, and **XV**, only the former was strongly active against Gram-positive bacteria, *Bacillus cereus* and *Staphylococcus aureus*, while compound **X** showed moderate inhibition zones against *Bacillus cereus* only. The other compounds were inactive against the two examined species of Gram-positive bacteria. Presumably, the presence of a cyano group in molecules **I** and **X** is responsible for their relatively high antimicrobial activity. Compounds **I**, **X**, and **XV** showed a strong to moderate activity against three species of fungi, namely *Candida albicans*, *Tricophyton rubrum*, and *Chrysosporium tropicum*. The relatively high antifungal activity of compound **XV** may be due to the presence of a fused triazine ring in its molecule. The other compounds showed no activity against the examined fungi species.

EXPERIMENTAL

The melting points were determined using a Kofler melting point apparatus and are uncorrected. The IR spectra were recorded on a Pye-Unicam SP3-100 instrument in KBr. The ^{1}H NMR spectra were obtained on a JNM-LA spectrometer (400 MHz) using tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV, ion source temperature 210°C) were recorded at the Chemistry Department, Norwegian University of Science and Technology (NTNU, Trondheim, Norway); the peak intensity ratios in the molecular ion clusters were consistent with the natural selenium isotope distribution. The elemental analyses were obtained on a Perkin–Elmer 240c analyzer; the results coincided with the calculated values within ±0.4%. The progress of reactions and the purity of products were monitored by TLC.

2-Amino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carbonitrile (I) was synthesized according to slightly modified procedure [14]: metallic selenium was added to a solution of cyclohexylidenemalonodinitrile and triethylamine in ethanol; the product was recrystallized from ethanol. No melting point and spectral data of compound **I** were given in [14]. Yield 4 g (80%), mp 190–192°C. IR spectrum, ν, cm^{-1}: 3420–3310 (NH_2), 2200 (OR). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.23 s (2H, NH_2), 1.65–1.75 m (4H, CH_2), 2.27–2.30 m (2H, CH_2), 2.47–2.61 m (2H, CH_2). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 22.26, 23.84, 26.03, 26.19, 85.21, 117.5, 121.10, 132.32, 167.50. Mass spectrum, *m*/*z* (I_{rel}, %): 226 (100) $[M]^+$.

2-Amino-3-(4,5-dihydro-1*H*-imidazol-2-yl)-4,5,6,7-tetrahydro-1-benzoselenophene (II). Carbon disulfide, 1 ml, was added dropwise to a mixture of 2.25 g (0.01 mol) of compound **I** and 5 ml of ethylenediamine. The mixture was heated for 48 h at 60°C on a water bath, cooled, and poured into ice water. The precipitate was filtered off, washed with water, and recrystallized from ethanol. Yield 1.5 g (56%), mp 170–172°C. IR spectrum, ν, cm^{-1}: 3400, 3300, 3150 (NH_2,

Antimicrobial activity of compounds **I**, **IX**, **X**, **XII**, **XIII**, and **XV** (inhibition zone, mm)[a]

Comp. no.	Gram-positive bacteria		Fungi		
	Bacillus cereus	*Staphylococcus aureus*	*Candida albicans*	*Tricophyton rubrum*	*Chrysosporium tropicum*
I	17	20	13	30	30
IX	–	–	–	–	–
X	11	–	12	23	23
XII	–	–	–	–	–
XIII	–	–	–	–	–
XV	–	–	11	20	27
Reference[b]	52	54	11	50	52

[a] Inhibition zone around the discs: 26–52 mm: very strong activity; 13–25 mm: strong activity; 7–13 mm: moderate activity; 0–7 mm: weak activity; dash denotes no activity.

[b] Chloramphenicol (5%, antibacterial activity); Terbinafine (5%, antifungal activity).

NH); 1600 (C=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 6.8 s (1H, NH, imidazole), 6.3 s (2H, NH_2), 3.40 s (4H, imidazole), 1.61–1.74 m (4H, CH_2), 2.27–2.31 m (2H, CH_2), 2.45–2.52 m (2H, CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 267 (100) $[M]^+$. Compound **IV** was isolated as by-product by fractional crystallization from ethanol.

2,3,8,9,10,11-Hexahydro[1]benzoselenopheno-[3,2-*e*]imidazo[1,2-*c*]pyrimidine (III). A mixture of 0.3 g (0.0011 mol) of compound **II**, 5 ml of triethyl orthoformate, and 0.2 ml of glacial acetic acid was heated for 4 h under reflux. The precipitate was filtered off and recrystallized from ethanol. Yield 0.2 g (66%), mp 270–272°C. IR spectrum: ν(C=N) 1610 cm^{-1}. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.1 s (1H, pyrimidine), 3.70 s (4H, imidazole), 1.61–1.74 m (4H, CH_2), 2.27–2.31 m (2H, CH_2), 2.45–2.52 m (2H, CH_2).

2,3,5,6,8,9,10,11-Octahydro[1]benzoselenopheno-[3,2-*e*]imidazo[1,2-*c*]pyrimidine-5-thione (IV). A mixture of 2 g (0.0074 mol) of compound **II**, 10 ml of carbon disulfide, and 20 ml of anhydrous pyridine was heated for 30 h on a water bath. The mixture was cooled, and the precipitate was filtered off and recrystallized from acetic acid. Yield 1 g (45%), mp >300°C. IR spectrum, ν, cm^{-1}: 3150 (NH), 1620 (C=N), 1140 (C=S). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.88 s (1H, NH), 3.85 s (4H, imidazole), 1.61–1.74 m (4H, CH_2), 2.27–2.31 m (2H, CH_2), 2.45–2.52 m (2H, CH_2). Found, %: S 10.11. $C_{12}H_{13}N_3SSe$. Calculated, %: S 10.32.

5-Phenyl-2,3,5,6,8,9,10,11-octahydro[1]benzo-selenopheno[3,2-*e*]imidazo[1,2-*c*]pyrimidine (V). Concentrated hydrochloric acid, 0.2 ml, was added to a mixture of 0.3 g (0.0011 mol) of compound **II** and 0.3 ml (0.003 mol) of benzaldehyde in 10 ml of anhydrous ethanol. The mixture was stirred for 8 h at 60°C, cooled, and neutralized with an aqueous solution of sodium carbonate. The precipitate was filtered off and recrystallized from dioxane. Yield 0.3 g (75%), mp 290–292°C. IR spectrum, ν, cm^{-1}: 3150 (NH), 1610 (OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.20–7.8 m (5H, C_6H_5), 6.7 s (1H, NH), 6.5 s (1H, 5-H), 3.90 s (4H, imidazole), 1.61–1.75 m (4H, CH_2), 2.27–2.30 m (2H, CH_2), 2.47–2.50 m (2H, CH_2).

5-Hydrazino-2,3,8,9,10,11-hexahydro[1]benzo-selenopheno[3,2-*e*]imidazo[1,2-*c*]pyrimidine (VI). A mixture of 2 g (0.0064 mol) of compound **IV**, 10 ml of hydrazine hydrate (excess), and 20 ml of ethanol was heated for 5 h under reflux. The mixture was cooled, and the precipitate was filtered off and recrystallized from ethanol. Yield 1.5 g (76%), mp 240–242°C. IR spectrum, ν, cm^{-1}: 3400–3150 (NH_2, NH), 1610 (OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.3 s (1H, NH), 6.3 s (2H, NH_2), 3.50 s (4H, imidazole), 1.61–1.75 m (4H, CH_2), 2.27–2.30 m (2H, CH_2), 2.47–2.50 m (2H, CH_2).

5,6,8,9,10,11-Hexahydro[1]benzoselenopheno-[3,2-*e*]imidazo[2,1-*c*][1,2,4]triazolo[3,4-*a*]pyrimi-dine (VII). A mixture of 0.3 g (0.97 mmol) of compound **VI** and 10 ml of triethyl orthoformate was heated for 4 h under reflux. The mixture was cooled, and the precipitate was filtered off and recrystallized from ethanol. Yield 0.2 g (66%), mp 280–282°C. IR spectrum: ν(C=N) 1620 cm^{-1}. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.3 s (1H, 1-H), 3.70 s (4H, imidazole), 1.64–1.76 m (4H, CH_2), 2.28–2.33 m (2H, CH_2), 2.47–2.55 m (2H, CH_2).

5,6,8,9,10,11-Hexahydro[1]benzoselenopheno-[3,2-*e*]imidazo[2,1-*c*]tetrazolo[5,1-*a*]pyrimidine

(VIII). A solution of 0.4 g of sodium nitrite in 5 ml of water was added dropwise under vigorous stirring at room temperature to a solution of 0.5 g (0.0016 mol) of compound **VI** in 10 ml of acetic acid. After the addition was complete, the mixture was stirred for an additional 5 h and neutralized with a solution of sodium carbonate, and the precipitate was filtered off and recrystallized from dioxane. Yield 0.3 (56%), mp 235–237°C. IR spectrum: ν(C=N) 1620 cm^{-1}.

4-Amino-5,6,7,8-tetrahydro[1]benzoselenopheno[2,3-*d*]pyrimidine (IX). A mixture of 0.5 g (0.0022 mol) of compound **I** and 10 ml of formamide was heated for 1 h under reflux. The mixture was cooled, and the precipitate was filtered off, washed with water, and recrystallized from aqueous dioxane. Yield 0.5 g (89%), mp 266–268°C. IR spectrum, ν, cm^{-1}: 3420–3310 (NH_2), 1620 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.44 s (1H, 2-H), 6.1 s (2H, NH_2), 1.62–1.79 m (4H, CH_2), 2.51–2.66 m (2H, CH_2), 3.31–3.40 m (2H, CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 253 (70) $[M]^+$.

2-Ethoxymethyleneimino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carbonitrile (X). A mixture of 1 g (0.0044 mol) of compound **I**, 10 ml of triethyl orthoformate, and 3 ml of acetic anhydride was heated on a water bath for 4 h at 60°C. The mixture was cooled, and the precipitate was filtered off and recrystallized from petroleum ether (bp 60–80°C). Yield 0.5 g (40%), mp 85–87°C. IR spectrum, ν, cm^{-1}: 2200 (C≡N), 1610 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.19 s (1H, N=CH), 4.29 q (2H, CH_2), 1.31–1.33 t (3H, CH_3), 1.20–1.36 m (4H, CH_2), 1.74–1.36 m (2H, CH_2), 2.50–2.70 m (2H, CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 282 (100) $[M]^+$.

1,2,3,4,5,6,7,8-Octahydro-1-benzoselenopheno-[2,3-*d*]pyrimidine-2,4-dithione (XI). Carbon disulfide, 2 ml, was added to a solution of 1 g (0.0044 mol) of compound **I** in 15 ml of pyridine. The mixture was heated for 10 h under reflux (on a water bath) and cooled, and the precipitate was filtered off and recrystallized from ethanol. Yield 0.5 g (38%), mp 240–242°C. IR spectrum, ν, cm^{-1}: 3150 (NH), 1140 (C=S). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.82 s (2H, NH), 1.60–1.82 m (4H, CH_2), 2.72–2.82 m (2H, CH_2), 3.21–3.38 m (2H, CH_2).

4-Imino-1,2,3,4,5,6,7,8-octahydro-1-benzoselenopheno[2,3-*d*]pyrimidine-2-thione (XII). A mixture of 2.25 g (0.001 mol) of compound **I** and 1.20 ml (0.01 mol) of phenyl isothiocyanate in 20 ml of pyridine was heated for 8 h under reflux. The mixture was cooled and poured into 50 ml of ice water, and the precipitate was filtered off and recrystallized from ethanol. Yield 1.5 g (44%), mp 230–232°C. IR spectrum, ν, cm^{-1}: 3170 (NH), 1140 (C=S). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.21 s (1H, NH), 8.82 s (1H, NH), 7.41–7.55 m (5H, C_6H_5), 1.60–1.82 m (4H, CH_2), 2.72–2.82 m (2H, CH_2), 3.21–3.38 m (2H, CH_2).

2-Acetylamino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carbonitrile (XIII). A mixture of 0.2 g (0.89 mmol) of compound **I** and 20 ml of acetic anhydride was heated for 10 h under reflux. The mixture was cooled, and the precipitate was filtered off and recrystallized from ethanol. Yield 0.12 g (52%), mp 218–220°C. IR spectrum, ν, cm^{-1}: 3150 (NH), 1690 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 9.63 s (1H, NH), 2.25–2.26 s (3H, CH_3), 1.77–1.78 m (4H, CH_2), 2.52 m (2H, CH_2), 2.65 m (2H, CH_2).

4-Chloro-5,6,7,8-tetrahydro[1]benzoselenopheno[2,3-*d*][1,2,3]triazine (XV). A solution of 0.3 g (4.3 mmol) of sodium nitrite in 5 ml of water was added over a period of 2 h under stirring and cooling with ice to a solution of 0.2 g (0.89 mmol) of compound **I** in a mixture of 10 ml of acetic acid and 3 ml of hydrochloric acid. The product was recrystallized from dioxane. Yield 0.15 g (63%), mp 125–127°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.62–1.79 m (4H, CH_2), 2.51–2.66 m (2H, CH_2), 3.31–3.40 m (2H, CH_2). Found, %: Cl 12.88. $C_9H_8ClN_3Se$. Calculated, %: Cl 13.02.

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