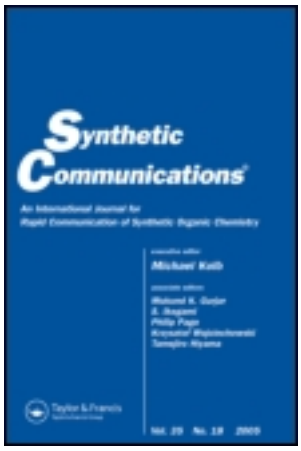

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Synthesis of 7-Azabenzisoselenazol-3(2H)-ones: A New Group of Selenium Containing Antimicrobials

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ABSTRACT

A convenient, general method for synthesis of various 2-substituted 7-azabenzisoselenazol-3(2H)-ones having pyridine ring condensed with selenazolone moiety is presented. It is based on the conversion of 2-chloronicotinic acid into 2-(chloroseleno)nicotinic acid chloride and its reaction with primary amines. The title compounds were found in the antimicrobial assay in vitro to be highly active against broad spectrum of bacteria and fungi.

Benzisoselenazol-3(2H)-ones are group of organoselenium compounds extensively studied during last two decades as biological response

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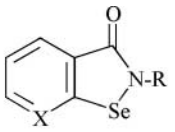
modifiers. The best known their representative is nontoxic ($LD_{50} = 6.8$ g/kg) 2-phenylbenzisoselenazol-3(2H)-one named ebselen (**1**) (Sch. 1). It is able to inactivate the oxygen species present in the living cells in the glutathione peroxidase-like way.[1,2] Different 2-substituted benzisoselenazol-3(2H)-ones were found as antiinflammatory agents, immunomodifiers, cytokine inducers, enzyme inhibitors, and virucides.[2,7] More than ten years ago ebselen has been shown to possess antibacterial activity against *Staphylococcus aureus*[8] and it has been postulated that the antibacterial activity of ebselen and other selenium compounds in vitro is due to their reactivity with an essential thiol group.[9] Recently ebselen, some other benzisoselenazolones and *o*-substituted diaryldiselenides have been evaluated for their antifungal and antibacterial properties.[10]

Among different benzisoselenazolones only two azabenzisoselenazolones (**2e** and **2f**), having pyridine ring in a place of benzene ring, are known. They have been obtained from nicotinamides by ortholithiation, then methylselenylation, and finally cyclization with formation of Se-*N* bond. The method used for their synthesis is limited to these compounds.[11] In our knowledge their biological activity has not been investigated. It seemed to be possible that introduction of nitrogen atom into benzene ring should made the molecule more polar and noncovalent interactions such/formation of hydrogen bonds between drug molecule and biological receptor should took place. Both of these factors might have an influence on the biological response in comparison to the ebselen.

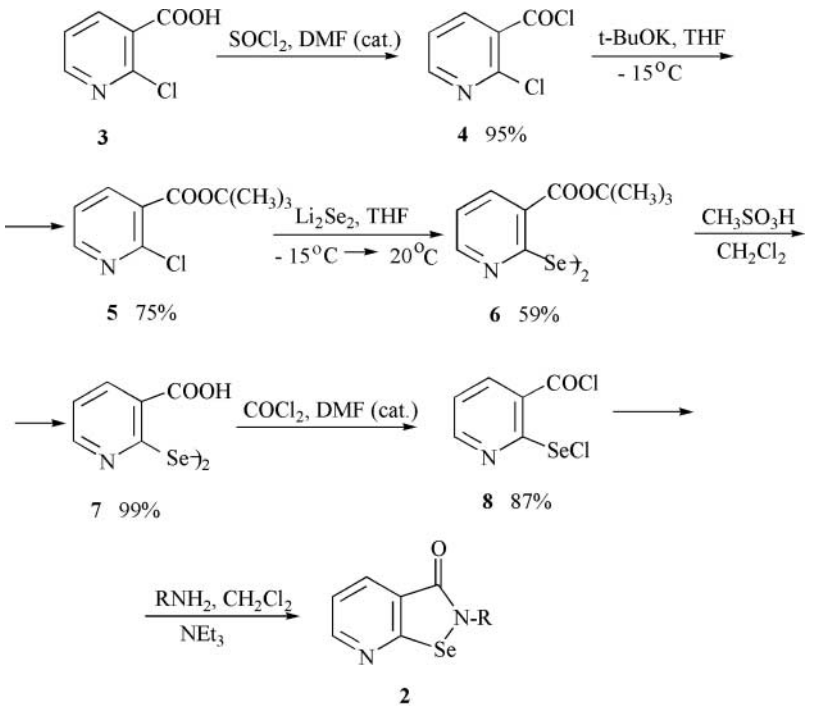
In this article we present a general method for synthesis 7-azabenzisoselenazol-3(2H)-ones (**2**) (Sch. 1) and report their appreciable biological activity against broad spectrum of bacteria and fungi.

The general strategy for synthesis of 7-azabenzisoselenazol-3(2H)-ones (**2**), presented in Sch. 2, is based on the conversion of 2-chloronicotinic acid (**3**) into 2-(chloroseleno)nicotinoyl chloride (**8**) and finally on the tandem acylation-selenylation of primary amino group, present in aminoalkanes or aminoarenes, with this reagent.



1 X= CH, R= PH
2 X= N, R= Ph and other substituents

Scheme 1.



R: H (**a**), Me (**b**), *n*-Pr (**c**), *t*-Bu (**d**), Hex (**e**), -Ph (**f**), 4-ClC_6H_4 (**g**), $-NPh_2$ (**h**), 2-Py (**i**), 5-Cl-(2-Py) (**j**)

Scheme 2.

Initially, 2-chloronicotinic acid (**3**) was converted to the acid chloride **4** in usual way with thionyl chloride in the presence of dimethylformamide as catalyst. The acid chloride **4** treated with potassium *tert*-butoxylate in dry tetrahydrofurane on the ice/salt bath gave *tert*-butyl-2-chloronicotinate (**5**). This oily ester could not be purified by distillation because of its thermal instability (decomposed ca. 120°C at 8 torr). Nevertheless ^{1}H NMR spectrum made the evidence of its purity and it was used in the next step of synthesis without purification. In the next step the chlorine atom in ester **5** was substituted with diselenide group and 2,2′-diselenobis(*tert*-butylnicotinate) (**6**) was obtained by the reaction of compound **5** with freshly prepared dilithium diselenide in dry tetrahydrofurane. Acid hydrolysis of ester **6** gave 2,2′-diselenobis(nicotinics acid) (**7**). For this purpose methanesulfonic acid

was used as hydrolyzing agents since other common acids were less active, the reaction proceeds more slowly, and yields of the acid were substantially lower. The reaction of acid **7** with thionyl chloride in the presence of catalytic amounts of dimethylformamide lead to 2-(chloroseleno)nicotinoyl chloride (**8**). The last step of the synthesis was similar to the tandem acylation-selenylation primary amino group with 2-(chloroseleno)benzoyl chloride reported in our earlier works.[4–7,12,13] The reaction of dichloride **8** and ammonia or corresponding aliphatic, or aromatic amine in dry dichloromethane at ca. -15°C resulted in formation of desired 7-azabenzisoselenazol-3(2H)-one (**2a**) or its 2-substituted alkyl and aryl derivatives **2b–2h.** In the same manner diazaanalogues of ebselen **2i** and **2j** were obtained. Both of them have one pyridine ring condensed with isoselenazolone moiety while the second pyridine ring is an substituent. Since in the reaction hydrochloric acid is eliminated, ammonia or amine was used in threefold excess although in some cases **2e–2j** triethylamine was applied as a base.

The positive results of the reaction of 2-(chloroseleno)nicotinoyl chloride (**8**) with primary aliphatic and aromatic amines lead to supposition that it could be employed as versatile reagent for tandem acylation-selenenylation of aminoacids, primary amides, and sulfonamides or compounds having active methylene groups similarly as earlier used its analogue 2-(chloroseleno)benzoyl chloride.[6,12,15]

The ebselen (**1**) and 7-azabenzisoselenazol-3(2H)-ones (**2a–j**) were tested against various bacteria and fungi strains (listed in Experimental) in vitro. Only **2a** and **2b** were active against gram-negative bacteria and none of them was active for *Sarcina lutea* strain. Most of them (**1**, **2a–f**, **h**) exhibited activity against *Staphylococcus aureus* (MIC = 16–512 μg/mL). Usually resistant sporulating rods *Bacillus* strains were very susceptible to the compounds **2a–e**, **h**. Their activity (MIC = 4–8 μg/mL) was substantially higher that found for ebselen (MIC = 16–128 μg/mL). The compounds tested were generally inactive against *Candida albicans* but the compounds **2a–e**, **h** strongly inhibited the growth of moulds—*Aspergillus niger*, *Penicillum chrysogenum*, and *Penicillum citrinum* (MIC = 2–32 μg/mL, for ebselen 128–256 μg/mL). The broadest activity spectrum and lowest MIC values were observed for the compounds **2a–c**. These results support our supposition that replacing of benzene ring in the benzisoselenazolone moiety by pyridine ring enhances the biological response. The more extended biological results and the details concerned to structure activity relationship will be published elsewhere.

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EXPERIMENTAL

General

Melting points: Digital Melting Point Apparatus Electrothermal IA 9100. ^{1}H NMR: Bruker 300-MHz spectrometer. IR (KBr pellets or CCl_4): Perkin-Elmer 2000 FT. All starting materials were purchased from Aldrich Chem. Co. and Fluka. Ebselen (**1**) was obtained according to ref.[4] Tetrahydrofurane was dried as reported in ref.[16] Dilithium diselenide was prepared directly before using from elemental lithium (0.36 g, 0.052 mol) and selenium powder (3.95 g, 0.050 mol) in the some way as reported in ref.[16]

The antimicrobial activities of tested compounds were evaluated by the agar dilution method.[17] Nutrient Agar and Mycological Agar were used for bacteria and fungi, respectively. Gram-positive bacterial species: *Staphylococcus aureus* PCM 1944, *Sarcina lutea* PCM 1947, *Bacillus* strains (*B. Subtilis* PCM 1949, *B. Cereus*, *B. Megaterium*, *B. Thuringensis*), and gram-negative bacterial species. *Escherichia coli* PCM 2057, *Serratia marcescens* PCM 549, *Pseudomonas putida* PCM 2124, and fungal strains: *Candida albicans*, *Aspergillus niger*, *Penicillium chrysogenum*, *Penicillium citrinum* were used for the test.

Synthesis of 2-Chloronicotinoyl Chloride (**4**)

A suspension of 2-chloro-nicotinic acid (**3**) (31.52 g, 0.2 mol) and dimethylformamide (5 drops) in thionyl chloride (200 mL) was refluxed in moisture-free conditions for 4.5 h. After this period the excess of thionyl chloride was evaporated in vacuo. The greasy residue was dissolved in dichloromethane (200 mL), decolorized with charcoal, and solvent was evaporated in vacuo. The solid residue recrystallized from hexane gave pure **4**. Yield 83% M.p. 39–44°C (ref.[18] 39–44°C).

Synthesis of *ter*t-Butyl 2-Chloronicotinate (**5**)

A solution of acid chloride **4** (33.5 g, 0.19 mol) in dry THF (50 mL) was added dropwise during 1.5 h period to magnetically stirred, and cooled on ice/salt bath, solution of potassium *tert*-butoxylate (22.45 g, 0.2 mol) in dry THF (150 mL). The reaction was continued for additional 1.5 h, most of the solvent (ca. 150 mL) was removed in vacuo and water (200 mL) was added to the residue. The mixture was extracted with

dichloromethane (3 × 75 mL), combined extracts were dried with sodium sulfate and the solvent was evaporated in vacuo. The residue was triturated with four portions of hexane (100, 75, 50, and 50 mL). Hexane was evaporated in vacuo and crude **5** was purified on silicagel column using dichloromethane as an eluent. Yield 75%. Oil decomposed ca. 120°C/8 Torr. IR (CCl_4) 1736, 1713 cm^{-1} (CO). ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 9H, CH_3), 7.30 (dd, 1H, $J = 7.7$ and 4.8 Hz, ArH), 8.05 (dd, 1H, $J = 7.7$ and 1.9 Hz, ArH), 8.46 (dd, 1H, $J = 4.8$ and 1.9 Hz, ArH). Anal. calcd. for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66, Cl, 16.59, N, 6.56. Found: C, 56.26; H, 5.79; Cl, 16.30; N, 6.63.

Synthesis of 2,2′-Diselenobis(*tert*-butyl) Nicotinate (**6**)

The solution of ester **5** (10.68 g, 0.050 mol) in dry THF (60 mL) was added dropwise for 1 h under argon into magnetically stirred freshly prepared suspension of dilithium diselenide (0.052 mol) in dry THF (40 mL) cooled on the ice salt bath. The reaction was continued for 72 h (finally at room temperature), the mixture was poured into ice (ca. 400 g), carefully mixed and precipitated elemental selenium was filtered off and washed with water. The filtrate was extracted with dichloromethane (3 × 50 mL), combined extracts were decolorized with charcoal, dried with sodium sulfate, and solvent was removed under reduced pressure. The residue was recrystallized from chloroform-hexane (1:1). Yield 59%. M.p. 190–195°C (decomposition). IR (KBr) 1682 cm^{-1} (CO). ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 18H, CH_3), 7.08 (dd, 2H, $J = 7.08$ and 4.7 Hz, ArH), 8.13 (dd, 2H, $J = 7.8$ and 1.8 Hz, ArH), 8.47 (dd, 2H, $J = 4.7$ and 1.8 Hz, ArH). Anal. calcd. for $C_{20}H_{24}N_2O_4Se_2$: C, 46.0; H, 4.70; N, 5.45. Found: C, 46.55; H, 4.60; N, 5.52.

Synthesis of 2,2′-Diselenobisnicotinic Acid (**7**)

Methanesulfonic acid (2.90 g, 30 mmol) was added to the solution of ester **6** (3.86 g, 7.5 mmol) in dichloromethane at room temperature and the reaction was continued for 12 days until the yellow mixture decolorized. Colorless solid was filtered off, suspended in water (150 mL) and filtered again (its color turned back to yellow), washed with water and methanol, dried in the air and recrystallized from DMSO-methanol (1:1). Yield 77%. M.p. 219–220°C (decomposition). IR (KBr): 1666 cm^{-1} (CO). ^1H NMR (DMSO-d_6) δ 7.34 (dd, 2H, $J = 7.6$ and 4.8 Hz,

ArH), 8.25 (d, 2H, $J = 7.6$ Hz, ArH), 8.59 (d, 2H, $J = 4.8$ Hz, ArH), 13.95 (bs, 2H, COOH). Anal. calcd. for $C_{12}H_8N_2O_4Se_2$: C, 35.84; H, 2.01; N, 6.97. Found: C, 35.72; H, 2.09; N, 6.78.

Synthesis of 2-(Chloroseleno)nicotinoyl Chloride (**8**)

A suspension of acid **7** (4.02 g, 10 mmol) in freshly distilled thionyl chloride (25 mL) and one drop of dimethylformamide was refluxed in moisture-free conditions for 8 h. After this period an additional portion of thionyl chloride (20 mL) and DMF (one drop) was added to the mixture and reaction was continued for 8 h. Thionyl chloride was removed under reduced pressure, the residue was dissolved in dry dichloromethane and solid was filtered off avoiding contact with air. From the filtrate dichloromethane was evaporated in vacuo and the residue solidified in the refrigerator was crude acid chloride **8** which directly was employed in the next step without purification since its low stability. Yield 87%. M.p. decomposed above 50°C. IR (KBr): 1660 cm^{-1} (CO). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, 1H, $J = 8.0$ and 4.7 Hz, ArH), 8.53 (dd, 1H, $J = 8.0$ and 1.7 Hz, ArH), 8.95 (dd, 1H, $J = 4.7$ and 1.7 Hz, ArH). Anal. for $C_6H_3Cl_2NOSe$ gave irreproducible results.

Syntheses of 7-Azabenzisoselenazol-3(2H)-ones (**2a–j**)

7-Azobenzisoselenazol-3(2H)-one (2a). The moisture-free gaseous ammonia was passed during 30 min through the solution of dichloride **8** (0.510 g, 2 mmol) in dry dichloromethane (40 mL) cooled on the ice/salt bath. After this period a solvent and excess of ammonia were removed under reduced pressure. Water (50 mL) was added to the residue and the mixture was carefully magnetically stirred. The solid was filtered off and recrystallized from dimethylformamide. Yield 64%. M.p. 258–259°C (decomposition). IR (KBr) 16.46 cm^{-1} (CO). ^{1}H NMR (300 MHz DMSO-d_6) δ 7.51 (dd, 1H, $J = 7.7$ and 4.7 Hz, ArH), 8.17(d, 1H, $J = 7.7$ Hz, ArH), 8.82 (d, 1H, $J = 4.7$ Hz, ArH), 9.34 (bs, 1H, NH). Anal. calcd. for $C_6H_4N_2OSe$: C, 36.20; H, 2.03; N, 14.06. Found: C, 36.06; H, 2.13; N, 14.19.

2-Methyl-7-azabenzisoselenazol-3(2H)-one (2b). The moisture-free gaseous methylamine was passed during 1 h through the solution of dichloride **8** (1.275 g, 5 mmol) in dry dichloromethane (60 mL) cooled on the ice/salt bath. After this period the reaction mixture was washed with water (3×50 mL), the layers were separated, the organic layer was dried with sodium sulfate and the solvent was removed under reduced

pressure. The product was separated by silica gel chromatography (trichloromethane), and recrystallized from dimethylsulfoxide-chloroform (1:1). Yield 72%. M.p 227–229°C (decomposition). IR (KBr) 1626 cm^{-1} (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.27 (s, 3H, CH_3), 7.49 (dd, 1H, $J = 7.7$ and 4.7 Hz, ArH), 8.13 (d, 1H, $J = 7.7$ Hz, ArH), 8.80 (d, 1H, $J = 4.7$ Hz, ArH). Anal. calcd. for $C_7H_6N_2OSe$: C, 39.08; H, 3.75; N, 13.02. Found: C, 39.23; H, 3.66; N, 13.10.

2-Propyl-7-azabenzisoselenazol-3(2H)-one (2c). Propylamine (0.488 g, 8.25 mmol) was dissolved in dry dichloromethane (10 mL) and then cooled to −15°C solution was added dropwise to magnetically stirred and cooled on ice/salt bath solution of dichloride **8** (0.637 g, 2.5 mmol) in dichloromethane (30 mL) for 30 min and the reaction was continued for additional 2 h. After this period the reaction mixture was washed with water (3 × 20) mL and the layers were separated. The organic layer was dried with sodium sulfate and the solvent was evaporated in vacuo. The product was separated from the residue by silica gel chromatography (chloroform-ethyl acetate (5:1)) and recrystallized from hexane. Yield 73%. M.p. 144–146°C (decomposition). IR (KBr) 1634 cm^{-1} (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.88 (t, 3H, $J = 7.3$ Hz, CH_3) 1.63 (sextet, 2H, $J = 7.2$ Hz, $\underline{CH_2}CH_3$), 3.70 (t, 2H, $J = 7.2$ Hz, $\underline{CH_2}CH_2$), 7.50 (dd, 1H, $J = 7.7$ and 4.7 Hz, ArH), 8.14 (dd, 1H, $J = 7.7$ and 1.5 Hz, ArH), 8.90 (dd, 1H, $J = 4.6$ and 1.5 Hz, ArH). Anal. calcd. for $C_9H_{10}N_2OSe$: C, 44.82; H, 4.18; N, 11.62. Found: C, 44.62; H, 4.25; N, 11.50.

2-*tert*-Butyl-7-azabenzisoselenazol-3(2H)-one (2d). It was obtained in the same manner as **2c** using *tert*-butylamine (0.603 g, 8.25 mmol) as a reagent. Yield 74%. M.p. 175–177°C (decomposition) (ref.[11] 173–175°C).

2-Cyclohexyl-7-azabenzisoselenazol-3(2H)-one (2e). It was obtained in the same manner as **2c** using cyclohexylamine (0.273 g, 2.75 mmol) as a reagent and triethylamine (0.556 g, 5.50 mmol) as a base. Recrystallized from ethyl ether. Yield 67%. M.p. 183–187°C. IR (KBr) 1639, 1650 cm^{-1} (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.15–1.22 (m, 1H, CH_2), 1.35–1.48 (m, 4H, CH_2), 1.60–1.64 (m, 1H, CH_2), 1.76–1.90 (m, 4H, CH_2), 4.27 (bs, 1H, CHN), 7.50 (dd, 1H, $J = 7.7$ and 4.7 Hz, ArH), 8.14 (dd, 1H, $J = 7.7$ and 1.2 Hz, ArH), 8.79 (dd, 1H, $J = 4.7$ and 1.2 Hz, ArH). Anal. calcd. for $C_{12}H_{14}N_2OSe$: C, 51.25; H, 5.02; N, 9.96. Found: C, 51.30; H, 5.10; N, 10.03.

2-Phenyl-7-azabenzisoselenazol-3(2H)-one (2f). It was obtained in the same manner as **2c** using aniline (0.256 g, 2.75 mmol) and triethylamine (0.556 g, 5.5 mmol). Recrystallized from chloroform-hexane (1:1). Yield 66%. M.p. 213–215°C (decomposition), (ref.[11] 209–211°C).

2-(4-Chloro)phenyl-7-azabenzisoselenazol-3(2H)-one (2g). It was obtained in the same manner as **2c** using 4-chloroaniline (0.351 g,

2.75 mmol) and triethylamine (0.556 g, 5.50 mL). Recrystallized from dimethylformamide. Yield 73%. M.p. 259–260°C (decomposition). IR (KBr) 1658 cm^{-1} (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.52 (d, 2H, $J = 6.8$ Hz, ArH), 7.57 (dd, 1H, $J = 7.8$ and 4.7 Hz, ArH), 7.69 (d, 2H, $J = 6.8$ Hz, ArH), 8.24 (dd, 1H, $J = 7.8$ and 1.8 Hz, ArH), 8.88 (dd, 1H, $J = 4.7$ and 1.8 Hz, ArH). Anal. calcd. for $C_{12}H_7ClN_2OSe$: C, 46.55; H, 2.28; N, 11.45. Found: C, 46.38; H, 2.34; N, 11.30.

2-(*N*,*N*-Diphenylamino)-7-azabenzisoselenazol-3(2H)-one(2h). To a suspension of diphenylhydrazine hydrochloride (0.552 g, 2.5 mmol) in dry chloromethane triethylamine (0.835 g, 8.75 mmol) was added dropwise under vigorous stirring, and cooled on the ice/salt bath. Thus obtained solution was treated with the solution of dichloride **8** (0.637 g, 2.50 mmol) in dry dichloromethane (30 mL) added dropwise during 30 min. After this period the reaction was continued for additional 3.5 h and the reaction mixture was worked up as for **2c**, using dichloromethane as an eluent for silica gel chromatography. Recrystallized from chloroform-hexane (1:1). Yield 28%. M.p. 161–162°C (decomposition). IR (KBr) 1663 cm^{-1} (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.07–7.10 (m, 6H, ArH), 7.31–7.36 (m, 4H, ArH), 7.53 (dd, 1H, $J = 7.7$ and 4.7 Hz, ArH), 8.24 (dd, 1H, $J = 7.7$ and 1.5 Hz, ArH), 8.86 (dd, 1H, $J = 4.7$ and 1.5 Hz, ArH). Anal. calcd. for $C_{18}H_{13}N_3OSe$: C, 59.02; H, 3.58; N, 11.47. Found: C, 59.23; H, 3.28; N, 11.24.

2-(2-Pyridinyl)-7-azabenzisoselenazol-3(2H)-one (2i). It was obtained in the same manner as **2c** using 2-aminopyridine (0.259 g, 2.75 mmol) and triethylamine (0.566 g, 5.50 mmol). The crude product precipitated from the reaction mixture was filtered, washed with dichloromethane (10 mL) and water (20 mL), dried in air and recrystallized from chloroform. Yield 72%. M.p. 221–223°C (decomposition). IR (KBr) 1651 cm^{-1} (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.23–7.24 (m, 1H, ArH), 7.54 (dd, 1H, 7.8 and 4.7 Hz, ArH), 7.90–7.96 (m, 1H, ArH), 8.25 (dd, 1H, $J = 7.8$ and 1.8 Hz, ArH), 8.42–8.45 (m, 1H, ArH), 8.57–8.61 (m, 1H, ArH), 8.88 (dd, 1H, $J = 4.7$ and 1.8 Hz, ArH). Anal. calcd. for $C_{11}H_7N_3OSe$: C, 47.84; H, 2.56, N, 15.22. Found: C, 47.65; H, 2.48; N, 15.11.

2-(5-Chloro-2-pyridyl)-7-azabenzisoselenazol-3(2H)-one (2j). It was obtained in the same manner as **2i** using 5-chloro-2-aminopyridine (0.354 g, 2.75 mmol) and triethylamine (0.566 g, 5.50 mmol). Recrystallized from dimethylformamide. Yield 83%. M.p. 258–260°C (decomposition). IR (KBr) 1663 cm^{-1} (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.54 (dd, 1H, $J = 7.8$ and 4.7 Hz, ArH), 8.04 (dd, 1H, $J = 8.7$ and 1.9 Hz, ArH), 8.24 (d, 1H, $J = 7.8$ Hz, ArH), 8.50 (s, 1H, ArH), 8.61 (d, 1H, $J = 8.7$ Hz, ArH), 8.87 (d, 1H, $J = 4.7$ Hz, ArH). Anal. calcd. for $C_{11}H_6ClN_3OSe$: C, 42.53; H, 1.95; N, 11.41. Found: C, 42.37; H, 1.88; N, 11.28.

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