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Research Article

Synthesis and Characterization of a New Five and Six Membered Selenoheterocyclic Compounds Homologues of Ebselen

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The discovery of the antioxidant activity of selenoenzyme glutathione peroxidase (GPx) has attracted growing attention in the biochemistry of selenium. Among molecules which mimic the structure of the active site of the enzyme, *N*-phenyl-1,2-benzisoselenazolin-3-one **1**, Ebselen, exhibited useful anti-inflammatory properties. It has been extensively investigated and has undergone clinical trials as an anti-inflammatory agent. Unfortunately, Ebselen exhibits relatively poor catalytic activity, prompting attempts to design more efficacious GPx mimetics that would retain his low toxicity while manifesting improved catalytic properties. In this context, novel 1,2-benzoselenazine and 1,2-benzoselenazols, which are five and six membered homologues of Ebselen were synthesized and characterized. One structure has been proven by single crystal X-ray crystallography.

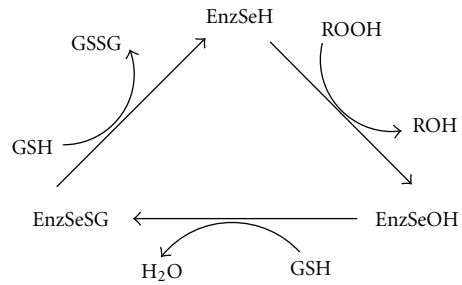
1. Introduction

The discovery of selenium as selenocysteine in the active site of the selenoenzyme glutathione peroxidase (GPx) has attracted growing attention in the biochemistry of selenium [1, 2]. The selenoenzyme acts as an antioxidant and catalyzes the reduction of harmful peroxides by glutathione, thus protecting lipid membranes against oxidative damage [3–9]. The enzyme catalytic site includes a selenocysteine residue in which the selenium undergoes a redox cycle involving the selenol (Enz-SeH) as the active form that reduces hydroperoxides and organic peroxides and the catalytic cycle is shown in Scheme 1. Thus, the selenol (EnzSeH) is first oxidized by the peroxide to the corresponding selenic acid (EnzSeOH), which reacts with GSH to afford a selenenyl sulfide intermediate (EnzSeSG). The latter undergoes further reaction with GSH, thereby regenerating the original selenol and producing oxidized glutathione (GSSG) as a byproduct [10–13].

Among molecules which mimic the structure of the active site of the enzyme, *N*-phenyl-1,2-benzisoselenazolin-3-one **1**, Ebselen (PZ51), exhibited useful anti-inflammatory properties [14, 15]. On the other hand, Ebselen contains a selenic moiety stabilized by intramolecular cyclisation in a cyclic *N*-aroyl selenamide and does not release selenium, as demonstrated by a ^{75}Se-labeling study, which result in its relatively nontoxic properties [16, 17]. The discovery of its anti-inflammatory and glutathione-peroxidase (GPx)-like activity has initiated numerous biochemical and pharmacological investigations as well as clinical trials as an antioxidant [18–21]. Similarly a study of the mechanism of the (GPx)-like activity of Ebselen has shown the formation in a catalytic cycle of various intermediates constituting different oxidation levels of the selenium atom [22, 23].

Several structural modifications of Ebselen including substituent effect and isosteric replacement have been proposed [24, 25]. For instance, diselenides and non-benzo-condensed isoselenazolidinone ring have been reported in the literature [26, 27].

Although it has attractive anti-inflammatory activity and low toxicity, Ebselen exhibits relatively poor catalytic activity, prompting attempts to design more efficacious GPx mimetics that would retain his low toxicity while manifesting improved catalytic properties. Hence, the design, synthesis,



EnzSeH = glutathione peroxidase
GSH = glutathione

Scheme 1: Catalytic cycle of glutathione peroxidase (GPx).

and evaluation of small-molecule selenium compounds that mimic the biological activity of GPx have been investigated by several groups, and selected examples **2** [28], **3** [29], **4** [30], and **5** [31] are presented in Scheme 2. Various diaryl diselenides [32–38] and certain types of tellurium compounds as well as dendrimeric and cyclodextrin-derived organochalcogen catalysts that emulate GPx have also been reported [39–46].

In the same context, our group focused on synthesizing new selenoheterocyclic compounds. The new heterocycles should preserve the Se–$C_{aromatic}$ bond to avoid the release of Se atoms and maintain the low toxicity of Ebselen. Secondly, the Se–N bond responsible for the GPx-like activity is retained.

2. Results and Discussion

The multistep synthesis of the novel benzoselenazine **10** is represented in Scheme 3. The starting molecule was *o*-chlorobenzonitrile **6**, which was easily transformed into ketone **7** by reaction with Grignard reagent. The incorporation of selenium was carried out by treatment of ketone **7** with methaneselenol in the presence of potassium carbonate yielding **8** in good yield. The oximination of selenide **8** was carried out using (n-$BuNO_2$, HCl) and 2-ethoxyethanol as solvent [47]. Oxime **9** was cyclized into the novel heterocycle 4*H*-benzo-1,2-selenazin-4-one **10** via Se-demethylation using trimethylsilyl polyphosphate (PPSE) [48].

The synthesis of the new selenoheterocycle **14** required the use of diketone **12**, which was obtained by oxidation of ketone **11** using SeO_2 as an oxidizing agent. The incorporation of selenium was carried out by treatment of diketone **12** with methaneselenol in the presence of potassium carbonate yielding **13**. The addition of 2 equivalents of bromine to a saturated solution of diketone **13** produced a yellow-orange precipitate. This precipitate, which is a result of quaternization of selenium by bromine, was treated by ammonia and purified to produce compound **14**, as determined by different spectroscopic techniques.

In order to further prove the structure of compound **14**, we attempted to independently synthesize the same compound starting from compound **11** according to the reactions outlined in Scheme 4. Thus, compound **14** was obtained by oxidation of novel heterocycle **16**, which in turn was prepared by bromination of ketone **15** followed by treatment with ammonia (Scheme 4).

In the same context, we describe a new strategy for the synthesis of a new heterocycle **20** analogue of Ebselen (Scheme 5).

2-Bromo-3-nitrobenzoic acid **17** was transformed *via* two steps to the hydrazide **18** and the selenium was incorporated as cited previously to give the selenide **19**. The treatment of 2-methylseleno-3-nitro-3′-N-phenylbenzohydrazide with excess of bromine produced a yellow-orange precipitate. It allowed unambiguous identification of the molecular formula of the compound **20** (Figure 1). The crystal data structure refinement for compound **20** has been reported previously [49].

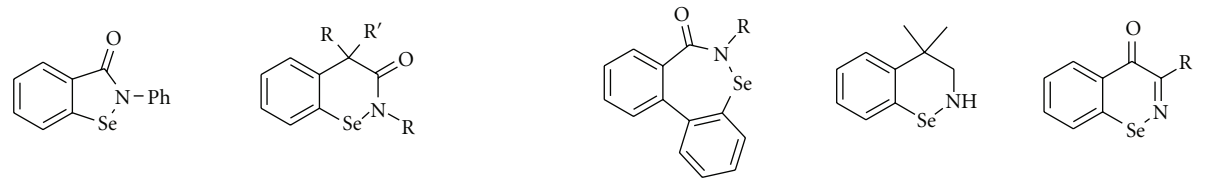
3. Conclusion

In order to evaluate their glutathione peroxidase-like activity, the synthesis of four novel heterocyclic compounds has been achieved. Namely, synthesis of 1,2-benzoselenazine-4-one derivative **10** which is six membered homologue of Ebselen PZ51 and three 1,2-selenazols **14**, **16** and **20**. The new compounds were fully characterized and one structure of them has been proven by single crystal X-ray crystallography.

4. Experimental

4.1. Synthesis of 1-(2-(Methylselanyl)phenyl)-3-phenylpropan-1-one (8). To a mixture of methaneselenol (1.2 mmol), K_2CO_3 (2 mmol) and DMF (40 mL), ketone **7** and (1 mmol) was added with stirring for a period of 30 minutes at 10°C. The mixture was refluxed under stirring for 6 h. After cooling, the mixture was washed with (2 × 10 mL) of water, extracted (3 × 20 mL) with toluene and dried over $MgSO_4$. After evaporation of the solvent, the obtained residue was purified by column chromatography over silica gel using (toluene-acetone 95 : 5) as eluent to provide compound **8** as yellow oil, yield 68%, IR (NaCl) ν_{max} 1664 cm^{-1} (C=O), ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.21 (s, 3H), 3.15 (t, 2H), 3.29 (t, 2H), 7.21–7.91 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 7.2 (CH_3), 31.0 (CH_2), 41.7 (CH_2), 124.9–142.1 (C arom), 199.8 (C=O), GCMS: *m/z* of >10% intensity 304 (M^+), 289, 199.

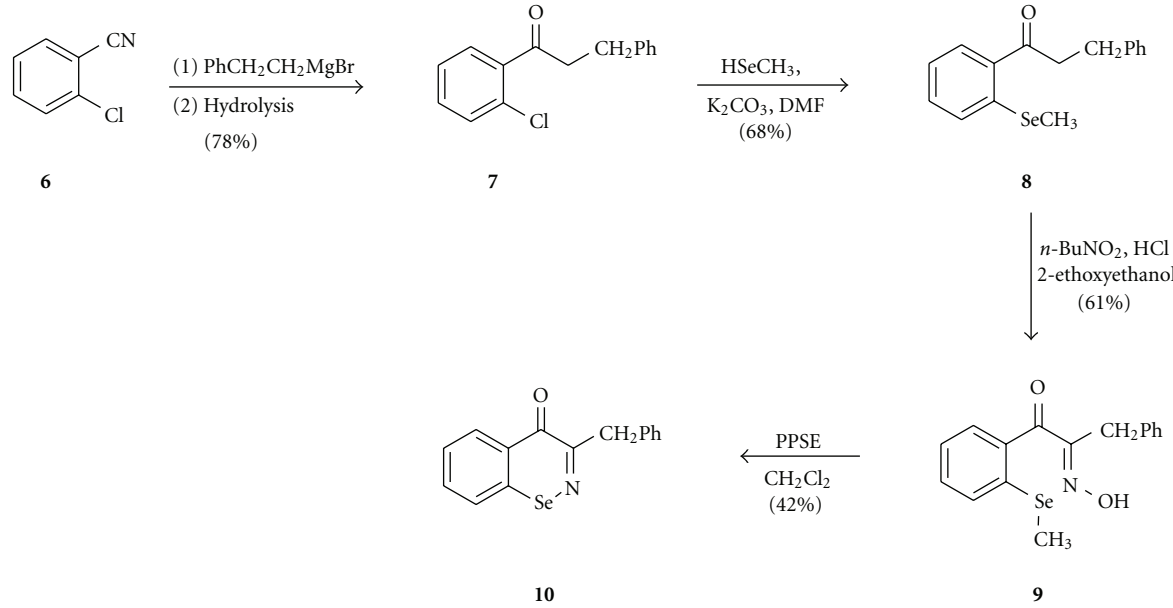
4.2. Synthesis of 2-(Hydroxyimino)-1-(2-(methylselanyl)phenyl)-3-phenylpropan-1-one (9). To a solution of ketone **8** (1 mmol) in ethoxyethanol (20 mL), concentrated HCl (3 mL) and n-$BuNO_2$ (1.2 mmol) were added with stirring at 0°C. The mixture was stirred for overnight at room temperature and then washed with 30 mL of dichloromethane. The organic layer was washed with a solution of NaOH (1 M) (2 × 10 mL) and dried over $MgSO_4$. After evaporation of the solvent, the obtained residue was purified by column chromatography over silica gel using (toluene-acetone 65 : 35) to provide compound **9** as yellow solid, yield 61%, Mp 132-133°C, IR (KBr) ν_{max} 3336 cm^{-1} (OH), 1650 cm^{-1} (C=O),



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

Ebselen (PZ51) R = H, CH_3, $CH_2C_6H_5$, C_6H_5; R′ = H, CH_3 R = H, CH_3, $CH_2C_6H_5$, C_6H_5 R = CO_2Et, CH_3, C_6H_5

Scheme 2



6 **7** **8** **10** **9**

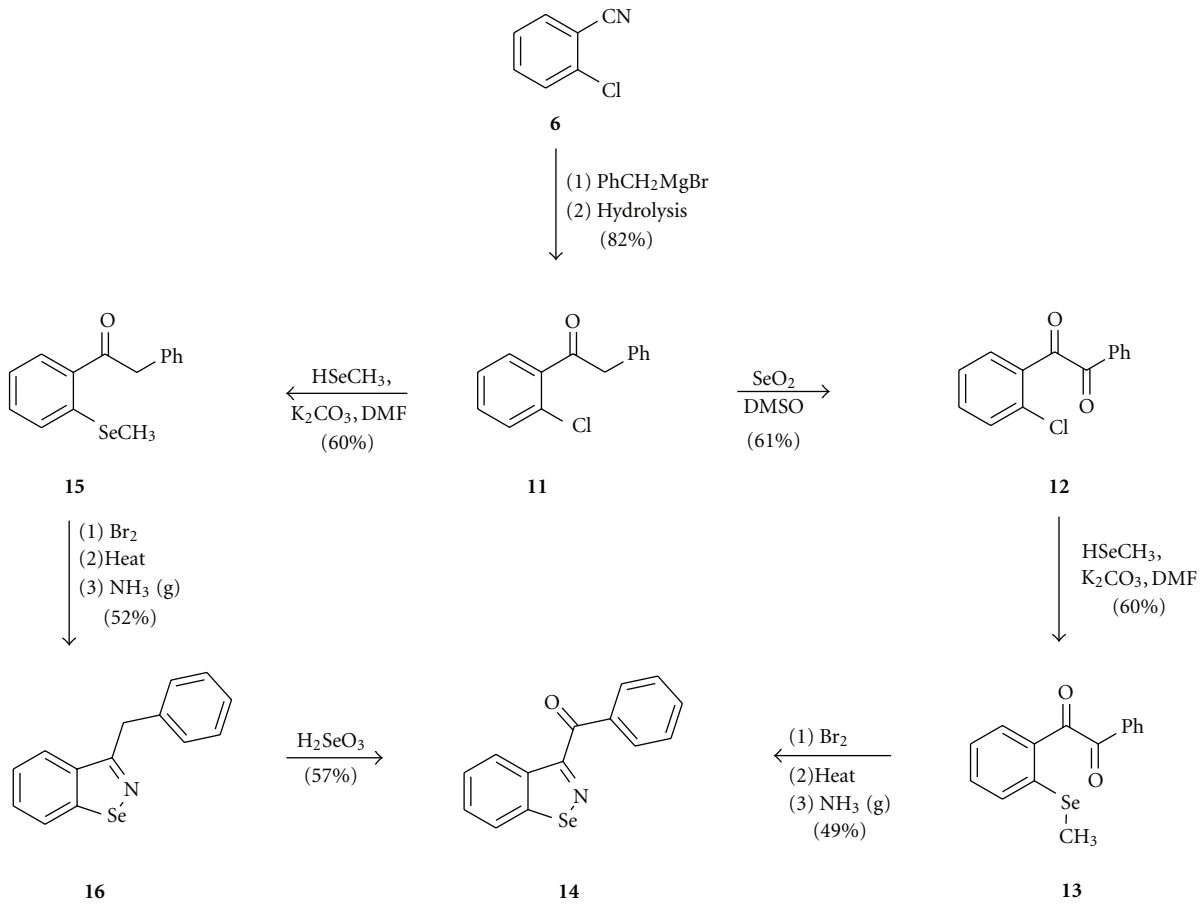
Scheme 3: The multistep synthesis of the novel 4*H*-benzo-1,2-selenazin-4-one **10**.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.21 (s, 3H), 4.08 (s, 2H), 7.27–7.49 (m, 9H, ArH), 9.16 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 7.3 (CH_3), 42.3 (CH_2), 124.6–148.2 (C arom), 192.3 (C=O), LCMS: *m/z* 334 (M^+).

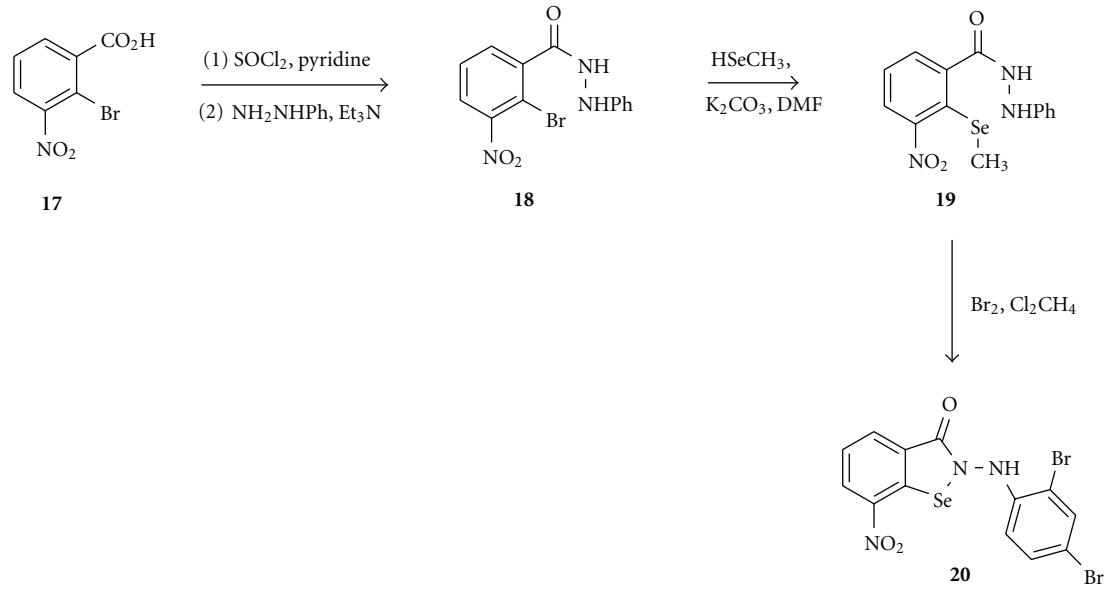
4.3. Synthesis of 3-Benzyl-1,2-benzoselenazin-4-one (10). A suspension of phosphorus oxide (7.05 mmol, 2 g) and hexamethyldisiloxane (14.9 mmol, 3.16 mL) in dichloromethane (15 mL) was refluxed for till complete dissolution (45 min). The mixture was evaporated under reduced pressure to provide trimethylsilyl polyphosphate (PPSE) as a viscous liquid which was then added to a solution of oxime **9** (0.69 mmol) in dichloromethane (10 mL). The mixture was refluxed under stirring for 8 h, then cooled and washed with water (2 × 10 mL) and dried over $MgSO_4$. After evaporation of the solvent, the obtained residue was purified by column chromatography over silica gel using (toluene-acetone 75 : 25) to provide heterocycle **10** as yellow solid, yield 42%, Mp 139–142°C, IR (KBr) ν_{max} 1668 cm^{-1} (C=O), ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.04 (s, 2H), 7.30–8.02 (m, 9H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 42.3 (CH_2), 127.2–153.2 (C arom), 193.2 (C=O), GCMS: *m/z* of >10% intensity 301 (M^+), 224, 156, Anal. Calcd for $C_{15}H_{11}NOSe$: C, 60.01.; H, 3.69; N, 4.67, found C, 59.75; H, 3.73; N, 4.74.

4.4. Synthesis of 1-(2-(Methylselanyl)phenyl)-2-phenylethane-1,2-dione (13). Compound **13** has been prepared from the diketone **12** according to the procedure described for compound **8**. Brown solid, yield 60%, Mp 115–119°C; IR (KBr) ν_{max} 1671 cm^{-1} (C=O), 1650 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.30 (s, 3H), 7.17–7.96 (m, 9H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 7.3 (CH_3), 125.2–135.5 (C arom), 194.6 and 195.6 (2 C=O); GCMS: *m/z* of >10% intensity 304 (M^+), 199, 156.

4.5. General Procedure for the Synthesis of Compounds 14 and 16. To a solution of compound **13** or **15** (1 mmol) in tetrachlorocarbon (20 mL), was added with stirring for a period of 30 minutes at 0°C, a solution of bromine (1.1 mmol) in tetrachlorocarbon (20 mL). The precipitate was refluxed



Scheme 4: The multistep synthesis of the novel benzisoselenazols **14** and **16**.



Scheme 5: The multistep synthesis of the novel 2-(2,4-dibromophenylamino)-7-nitrobenzisoselenazol-3-one **20**.

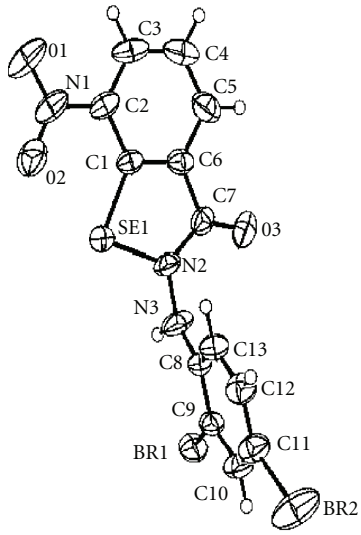


Figure 1: Crystal structure of compound **20**.

in dichloromethane (30 mL) under stirring for 1 h. After cooling, the mixture was saturated with a gaz ammonia flow. The insoluble substances were filtered and the solution was concentrated under reduced pressure. The obtained residue was purified by column chromatography over silica gel (toluene-acetone 95 : 5) to provide compounds **14** and **16**.

1,2-Benzoselenazol-3-yl(phenyl)methanone (14). This compound was obtained as yellow solid, yield 49%, Mp 75–79°C, IR (KBr) ν_{max} 1660 cm^{-1} (C=O), ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.47–8.53 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 123.1–145.5 (C arom), 197.8 (C=O); GCMS: *m/z* of >10% intensity 287 (M^+), 259, 282; Anal. Calcd for $C_{14}H_9NOSe$: C, 58.76.; H, 3.17; N, 4.89, found C, 58.87; H, 3.64; N, 4.81.

3-Benzyl-1,2-benzoselenazole (16). This compound was obtained as green oil; yield 52%, IR (NaCl) ν_{max} absence of (C=O), ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.41–8.49 (m, H arom), ^{13}C NMR (100 MHz, $CDCl_3$): δC 127.0–137.7 (C arom), GCMS: *m/z* of >10% intensity 273 (M^+), 193, 164; Anal. Calcd for $C_{14}H_{11}NSe$: C, 61.77.; H, 3.69; N, 5.15, found C, 61.86; H, 3.58; N, 4.08.

4.6. Synthesis of 2-(2,4-Dibromophenylamino)-7-nitrobenzisoselenazol-3-one (20). To a solution of hydrazide **19** (1 mmol) in dichloroethane (20 mL), bromine (3 mmol) was added with stirring for a period of 2 h at 0°C. After evaporation of the solvent, the obtained residue was purified by column chromatography over silica gel using (toluene) to provide compound **20** as brown solid, yield 78%, Mp 146–149°C, IR (KBr) ν_{max} 3269 cm^{-1} (NH), 1671 cm^{-1} (C=O), ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.19 (s, 1H), 6.54–7.22 (m, 5H), 8.21–8.56 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 110.1–143.7 (C arom), 167.3. (C=O); GCMS: *m/z* of >10% intensity 251, 170; Anal. Calcd for $C_{13}H_7Br_2N_3O_3Se$: C, 31.74.; H, 1.43; N, 8.54, found C, 31.93; H, 1.40; N, 8.47.

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