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Synthesis of 4*H*-benzo[*e*]-1,2-selanazin-4-one derivatives: a new heterocyclic ring system

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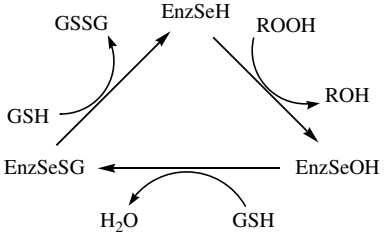
Abstract—The synthesis of novel 1,2-benzoselenazin-4-ones which are six-membered homologues of ebselen, is described in order to evaluate their glutathione peroxidase-like activity.

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] The selenoenzyme acts as an antioxidant and catalyzes the reduction of harmful peroxides by glutathione, thus protecting lipid membranes against oxidative damage.[2] 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. The selenol is oxidized to the selenenic acid (Enz-SeOH), which reacts with reduced glutathione (GSH) to form the selenenyl sulfide adduct (Enz-SeSG). A second glutathione then regenerates the active form of the enzyme by attacking the sulfide to form oxidized glutathione (GSSG) (Scheme 1).[3]



Scheme 1.

Among molecules which mimic the structure of the active site of the enzyme, *N*-phenyl-1,2-benzisoselenazolin-3-one **1**, ebseslen (PZ51), exhibited useful anti-inflammatory properties.[4] It generates a selenenic moiety stabilized by intramolecular cyclization in a cyclic *N*-aroyl selenamide. Ebselen does not release selenium, as demonstrated by a ^{75}Se-labeling study,[5] which results in its relatively non-toxic properties. 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.[6,7] 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.[8]

Several structural modifications of ebselen, including substituent effects and isosteric replacement, have been proposed.[9] For instance, diselenides and non-benzo condensed isoselenazolidinone rings have been reported in the literature.[10,11]

Nevertheless, its poor solubility remains a problem for optimal therapeutic development. In order to enhance its solubility and to increase its activity, research has been focused on the modification of the structure of ebselen. Hence, the design, synthesis, and evaluation of small-molecule selenium compounds that mimic the biological activity of GPx have been investigated by

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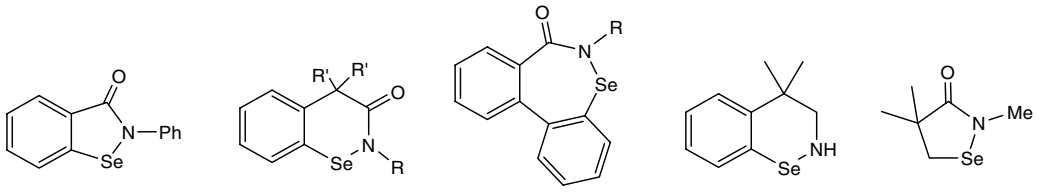


1 Ebselen (PZ51)

2 R= H, CH_3, $CH_2C_6H_5$, C_6H_5; R'= H, CH_3

3 R= H, CH_3, $CH_2C_6H_5$, C_6H_5

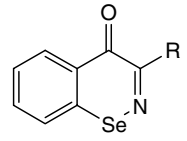
4

5

Chart 1.

several groups, and selected examples **2**,[12] **3**,[13] **4**[14] and **5**[15] are presented in Chart 1. Various diaryl diselenides[16] and certain types of tellurium compounds as well as dendrimeric and cyclodextrin-derived organochalcogen catalysts that emulate GPx have also been reported.[17–19]

In the same context, we describe here the synthesis of novel enlarged ebselen-like ring compounds, 4*H*-benzo[*e*]-1,2-selenazin-4-ones **6** (Scheme 2). The new structure contains an additional planar carbon between the nitrogen atom and the carbonyl group in the framework of ebselen. The structure 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. Thirdly, the carbonyl group with the double bond increases the electrophilic character of selenium which is necessary for the bioactivity of ebselen.



6

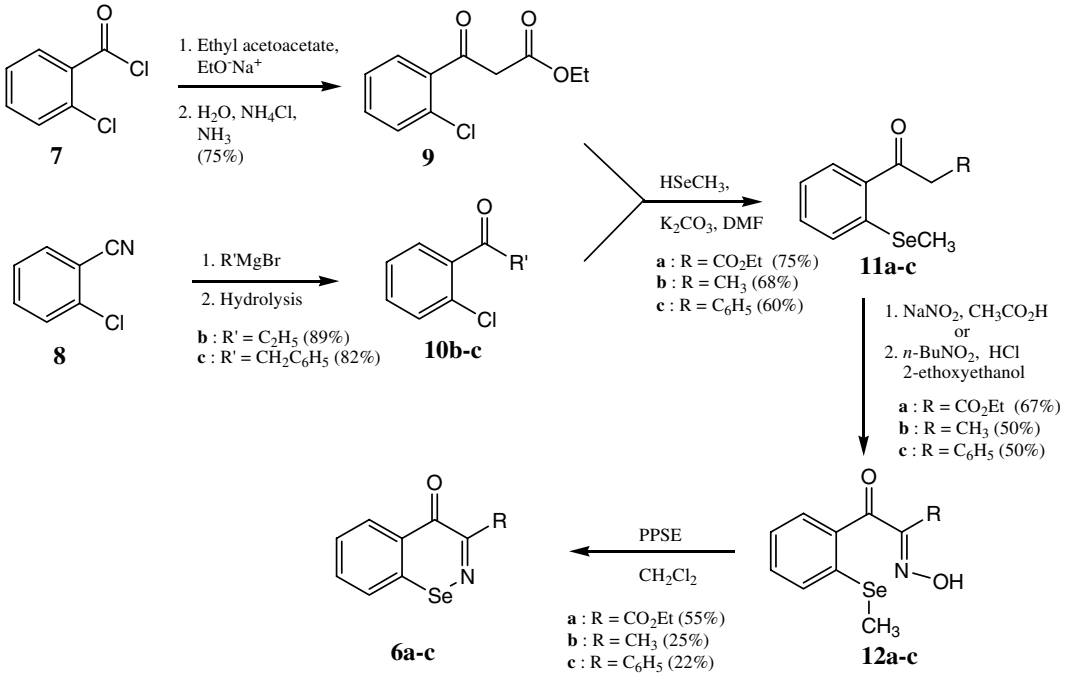
R= CO_2Et, CH_3, C_6H_5

Scheme 2.

To the best of our knowledge, only one reference describing the synthesis of ethoxycarbonyl-1,2-benzothiazine-4-one has been reported,[20] as a sulfur-containing heterocyclic homologue to one of our synthesized compounds **6a** (Scheme 3).

The starting molecules were *o*-chlorobenzoyl chloride **7** and *o*-chlorobenzonitrile **8**. Treatment of benzoyl chloride **7** with ethyl acetoacetate in the presence of sodium ethanoate followed by hydrolysis gave β-ketoester **9**. On the other hand, benzonitrile **8** was easily transformed into ketones **10b–c** by reaction with Grignard reagents.

The incorporation of selenium was carried out by treatment of β-ketoester **9** and ketones **10** with methaneselenol in the presence of potassium carbonate yielding **11a–c** in good yields.[21]



Scheme 3.

Selenide **11a** was nitrosated with $NaNO_2$, CH_3CO_2H resulting in a good yield of oxime **12a**.[22] The oximination of ketones **11b–c** was difficult using similar conditions, however, when this reaction was performed using (n-$BuNO_2$, HCl) and 2-ethoxyethanol as a solvent,[22] oximes **12b–c** were successfully obtained.[23]

Oximes **12a–c** were cyclized into 4*H*-benzo[*e*]-1,2-selenazin-4-ones **6a–c**[24] via Se-demethylation using trimethylsilyl polyphosphate (PPSE).[25,26]

The glutathione peroxidase GPx-like activity and antioxidant properties have been examined for compound **6a** and compared to ebselen as a control drug.[27] The kinetic method showed that **6a** increased the rate of the catalytic reduction of H_2O_2 more than ebselen, as monitored by the increase of the UV absorption at 305 nm due to the formed diphenyl disulfide (PhSSPh). However, **6a** inhibited the formation of the peroxidized lipid derived from the reaction of hydroxyl radicals with linoleic acid using radiation-induced lipid peroxidation. The evaluation of the antioxidant activity showed that ebselen and **6a** have the same inhibitory effect on the formation of ABTS radical cation in the ABTS/MetMb/H_2O_2 system. On the other hand, according to EPR spin trapping, **6a** exhibited a slightly lower protection of glutathione from the oxidant attack by the H_2O_2/HPR couple compared to ebselen.

The synthesis of novel 1,2-benzoselenazin-4-ones, which are six-membered homologues of ebselen, has been achieved. The evaluation of the glutathione peroxidase GPx-like activity and antioxidant properties of a selected product **6a** gave satisfactory results. The biological tests for the other compounds are under investigation.

Acknowledgment

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21. Characterization of compounds **11a–c**: **11a**: yellow oil, IR (NaCl) ν_{max} 1738 (C=O) and 1664 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.18 (t, $J = 7$, 3H), 2.14 (s, 3H), 3.92 (s, 2H), 4.12 (q, $J = 7$, 2H) 7.22–7.86 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 7.1 (CH_3), 14.8 (CH_3), 47.2 (CH_2), 62.1 (CH_2), 124.9 (C), 126.2 (CH), 127.5 (CH), 131.2 (CH), 133.4 (CH) 140.9 (C), 168.1 (C=O), 193.4 (C=O);

GCMS: *m/z* of >10% intensity 286 (M^+), 199; exact mass calcd for $C_{12}H_{14}O_3Se$ 286.0108, found 286.0092. Compound **11b**: yellow oil, IR (NaCl) ν_{max} 1664 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.22 (t, $J = 7.1$, 3H), 2.18 (s, 3H), 3.08 (q, $J = 7.1$, 2H) 7.22–7.94 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 7.1 (CH_3), 9.0 (CH_3), 32.9 (CH_2), 124.8 (C), 126.6 (CH), 127.7 (CH), 132.3 (CH), 134.2 (CH), 139.6 (C), 202.0 (C=O); GCMS: *m/z* of >10% intensity 228 (M^+), 213, 184; exact mass calcd for $C_{10}H_{12}OSe$ 228.0053, found 228.0070. Compound **11c**: yellow solid; mp 98–102 °C; IR (KBr) ν_{max} 1660 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.20 (s, 3H), 4.31 (s, 2H) 7.24–8.08 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 7.3 (CH_3), 46.7 (CH_2), 125.0 (C), 126.8 (CH), 127.9 (CH), 128.2 (CH), 128.4 (CH) 129.8 (CH), 130.1 (CH) 130.4 (CH) 133.3 (CH), 136.2 (CH), 138.5 (C), 140.6 (C), 199.8 (C=O); GCMS: *m/z* of >10% intensity 290 (M^+), 274, 245, 199; exact mass calcd for $C_{15}H_{14}OSe$ 290.0210, found 290.0230.

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23. Characterization of compounds **12a–c**: **12a**: yellow solid; mp 106–110 °C; IR (KBr) ν_{max} 3192 (OH), 1738 (C=O) and 1664 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) 1.20 (t, $J = 7$, 3H), 2.26 (s, 3H), 4.24 (q, $J = 7$, 2H), 7.36–7.69 (m, 4H) and 13.06 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 6.8 (CH_3), 14.7 (CH_3), 63.4 (CH_2), 124.9 (C), 126.5 (CH), 127.8 (CH), 131.5 (CH), 133.7 (CH) 140.9 (C), 160.1 (C), 165.2 (CO), 195.7 (CO); LCMS: *m/z* 316 ($M+H^+$); exact mass calcd for ($M+H^+$) $C_{12}H_{14}NO_4Se$ 316.0088, found 316.0095. Compound **12b**: yellow solid; mp 128–131 °C; IR (KBr) ν_{max} 3367 (OH), 1675 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) 2.33 (s, 3H), 2.41 (s, 3H), 7.36–7.69 (m, 4H), 12.92 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 6.8 (CH_3), 14.6 (CH_3), 125.3 (C), 127.9 (CH), 129.2 (CH), 132.0 (CH), 134.2 (CH), 141.6 (C), 158.6 (C), 188.2 (CO); LCMS: *m/z* 258 ($M+H^+$); exact mass calcd for ($M+H^+$) $C_{10}H_{12}NO_2Se$ 258.0033, found 258.0040. Compound **12c**: yellow solid; mp 109–112 °C; IR (KBr) ν_{max} 3388 (OH), 1673 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) 2.19 (s, 3H), 7.19–8.45 (m, 9H), 12.88 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 7.3 (CH_3), 125.2 (C), 128.2 (CH), 128.9 (CH), 129.0 (CH), 129.4 (CH), 131.0 (CH), 131.5 (CH), 132.0 (CH), 134.1 (C), 134.5 (CH), 136.0 (C), 159.7 (C), 190.3 (CO); LCMS: *m/z* 320 ($M+H^+$); exact mass calcd for ($M+H^+$) $C_{15}H_{14}NO_2Se$ 320.0190, found 320.0223.
24. All heterocycles **6** are new and gave satisfactory elemental analyses within 0.1% and gave correct mass spectra (based on ^{80}Se). Heterocycles **6** were recrystallized from a mixture of ligroïne and toluene except for **6c** (CH_2Cl_2/ligroïne). (b) Characterization of compounds **6a–c**: **6a**: yellow solid; mp 85–89 °C; IR (KBr) ν_{max} 1731 (C=O) and 1668 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, $J = 7$, 3H), 4.38 (q, $J = 7$, 2H), 7.45–8.42 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.9 (CH_3), 62.2 (CH_2), 124.2 (C), 127.6 (CH), 128.9 (CH), 131.9 (CH), 134.2 (CH), 145.9 (C), 159.9 (C), 164.7 (CO), 170.7 (CO); GCMS: *m/z* of >10% intensity 283 (M^+), 238, 210, 182, 156; exact mass calcd for $C_{11}H_9NO_3Se$ 282.9748, found 282.9727. Anal. Calcd for $C_{11}H_9NO_3Se$: C, 46.82; H, 3.22; N, 4.96, found C, 46.89; H, 3.18; N, 5.03. Compound **6b**: yellow solid; mp 119–123 °C; IR (KBr) ν_{max} 1674 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.17 (s, 3H), 7.59–8.91 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.8 (CH_3), 126.5 (C), 128.3 (CH), 129.9 (CH), 132.3 (CH), 134.1 (CH), 141.1 (C), 159.3 (C), 191.7 (CO); GCMS: *m/z* of >10% intensity 225 (M^+), 184, 156; exact mass calcd for C_9H_7NOSe 224.9693, found 224.9685. Anal. Calcd for C_9H_7NOSe: C, 48.23; H, 3.15; N, 6.25. Found: C, 48.32; H, 3.29; N, 6.14. Compound **6c**: yellow solid; mp 158–161 °C; IR (KBr) ν_{max} 1671 cm^{-1}(C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.30–8.02 (m, 9H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 127.0 (C), 128.7 (CH), 129.1 (CH), 129.5 (CH), 130.0 (CH), 130.9 (CH), 131.3 (CH), 131.8 (CH), 134.1 (CH), 134.5 (C), 137.7 (C), 159.2 (C), 194.1 (CO); GCMS: *m/z* of >10% intensity 287 (M^+), 184, 156; exact mass calcd for $C_{14}H_9NOSe$ 286.9849, found 286.9861. Anal. Calcd for $C_{14}H_9NOSe$: C, 58.76; H, 3.17; N, 4.89. Found: C, 58.65; H, 3.21; N, 4.94.
25. A suspension of phosphorus oxide (2 g, 7.05 mmol) in dichloromethane (15 ml) and hexamethyldisiloxane (3.16 ml, 14.9 mmol) was refluxed until complete dissolution (45 min) and the mixture was evaporated to provide trimethylsilyl polyphosphate (PPSE) as a viscous liquid. PPSE was added to a solution of oximes **12a–c** (0.69 mmol) in dichloromethane (10 ml). The mixture was refluxed under stirring for 8 h, then cooled and washed with (2 × 10 ml) water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue obtained was chromatographed over silica gel (toluene–acetone 75:25) to provide heterocycles **6a–c**.
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