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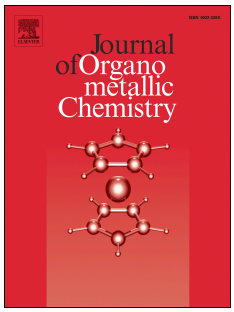

Hydrophobicity and glutathione peroxidase-like activity of substituted salicyloyl-5-seleninic acids: Re-investigations on aromatic selenium compounds based on their hydrophobicity

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Hydrophobicity and glutathione peroxidase-like activity of substituted salicyloyl-5-seleninic acids: re-investigations on aromatic selenium compounds based on their hydrophobicity

Sun-Chol Yu[a,b]*, Dong-Myong Ri[a], Hartmut Kühn[b]

*a. Faculty of Pharmacy, Pyongyang Medical College, **Kim Il Sung** University, Ryomyong Str., Pyongyang, DPR of Korea.*
b. Institute of Biochemistry, University Medicine Berlin-Charité, Chariteplatz 1, D-10117 Berlin, Germany

Previously we have shown that some of 5-selenized salicylic acid derivatives exhibit glutathione peroxidase (GPx)-like activities higher than or equal to ebselen [Yu et al., *Chem. Eur. J.*, 2008, **14**, 7066; *Org. Biomol. Chem.*, 2010, **8**, 828]. For understanding the absence of GPx-like activity of the homologue of 5-seleninic anhydride of salicyloylglycine with a loger side chain, we have further synthesized 19 new derivatives (5-seleninic acids of methyl or phenyl salicylates, *N*-salicyloyl ω-carboxyalkylamines or *N*-salicyloyl alkyl/phenyl amines, and some of their diselenides). Some of the 5-seleninic acids which carry long side chains or cyclohexyl group have exerted no GPx–like activity, irrespective of whether they are derived from ω-carboxyalkylamines or simple alkylamines. Such lacks of GPx-like activity let us quantitatively relate the GPx-like activities of the congeners of the above 3 series with their hydrophobicity (ClogP), which showed satisfactory correlations in each series. The molecular hydrophobicity was then extensively applied to diverse known aromatic selenium GPx mimics including diaryl diselenides and ebselen derivatives to explain their GPx-like activities in comparably quantitative mode, which could be helpful in designing new improved GPx mimic analogues in each series.

Keywords: Organoselenium compound, Antioxidant, Glutathione peroxidase-like activity, Partition Coefficient, Hydrophobicity, QSAR

1. Introduction

Selenium, an essential trace element for human health [1], has been of great significance in pathogenesis of many fatal diseases such as Keshan disease [2], cancer [3], etc. Selenium is incorporated into selenocysteine which functions as a re-dox active site of many selenoenzymes [4] including GPx. GPx is one of the most important antioxidant enzymes in mammals, which catalyses reduction of hydrogen peroxide and lipid peroxide, using glutathione (GSH) as a reductant [5,6]. During several decades, a variety of organoselenium compounds have been appeared as possible GPx mimics, but there are only a few leads superior to ebselen, a "standard" of organoselenium GPx mimics [7].

We have previously synthesized a new 5-seleninic anhydride of salicyloylglycine (**1** in Fig. 1) which exhibited higher GPx-like activity than ebselen and inhibited plant and mammalian 12/15-lipoxygenase (LOX) [8]. Further synthesized 5-selenized salicylic acid derivatives showed not only selective inhibition against 5-LOX but also GPx-like activities superior or similar to the lead compound (**1**) [9]. Interestingly, only one derivative (**2**) with a long side chain showed no detectable GPx-like activity [9].

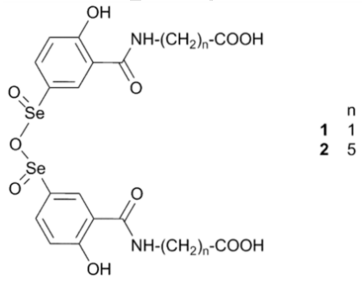


Fig. 1 5-seleninic anhydrides of *N*-salicyloyl ω-carboxyalkylamines published earlier.

* Corresponding author.
E-mail address: ryongnam34@yahoo.com

To our knowledge of structure-activity relationship in a series of homologues, elongation of a side chain might result in steric and hydrophobic effect on certain biological activity. Steric effects of substituents in aromatic selenium GPx mimics have been discussed mainly in the cases of *ortho*-substituted analogues [7], but the effect of molecular hydrophobicity has not been mentioned yet. Because the elongation of substituents in our salicyloyl-derived GPx mimics occurs in *meta*-position to seleninic acid, their catalytic reactions might not be affected by steric hindrance of substituents. Actually, molecular hydrophobicity does not directly influence on GPx-like reaction mechanism, but the reaction rate could depend on it as the catalytic assay runs in certain solvents (e.g. phosphate buffer solution or CH_2Cl_2/MeOH). We, therefore, continued to synthesize 19 new derivatives with carbon side chains of different lengths to relate their hydrophobicity with their GPx-like activities.

The result that not the simple side chain elongation but the change in molecular hydrophobicity could affect the catalytic reactivity of our GPx mimics has encouraged us to apply this hydrophobic effect to some of known aromatic selenium GPx mimics, including diaryl diselenides and ebselen derivatives.

2. Experimental

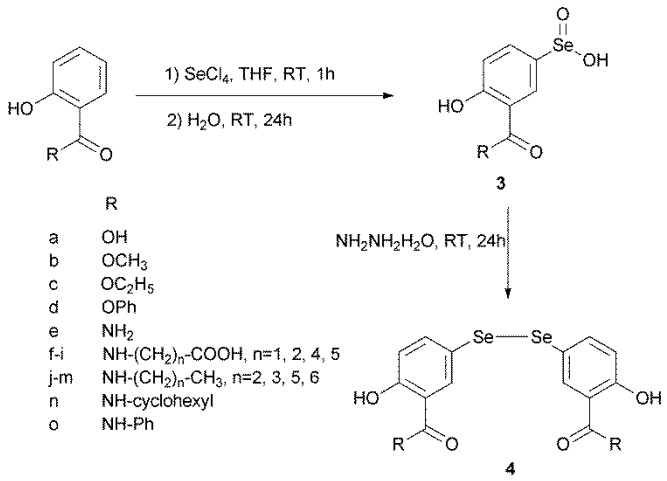
2.1. Chemicals and instruments

Some starting reagents such as methyl salicylate, phenyl salicylate (salol), salicylamide, salicylanilide and $SeCl_4$ were purchased from Merck and Sigma-Aldrich and commercially unavailable reagents were synthesized by the reaction of methyl salicylate with corresponding amines. All the solvents were of extra pure grade from Roth (Germany). ^{1}H and ^{13}C NMR spectra were recorded on a Brucker Biospin AV 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) or 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) by using d_6-DMSO as a solvent. For **3m** and **4m**, d_6-D_2O+KOH was used as a solvent because of its getting dark in d_6-DMSO. Chemical shift values (δ) are reported in ppm downfield from

TMS (δ =0.0 ppm) as internal standard. ^{77}Se NMR spectra were recorded by using a Brucker Avance II 300 instrument (57.2 MHz) in d_6-DMSO (dimethylselenide as external standard). HR-MS recording was done on a Finnigan Thermo Scientific LTQ OrbitrapXL (ESI) in MeOH. Elemental analysis was carried out on HEKAtech EURO EA, vario EL. Some IR spectra were recorded on a Nicolet Avatar 360 FT-IR. Kinetic measurements were performed on a Shimadzu UV-2102 spectrophotometer.

2.2. General procedure for 5-selenization of salicyloylamines

Synthetic procedure followed Scheme 1. A solution of $SeCl_4$ (5 mmol, 1.107 g) in THF (10mL) was added to a solution of salicyloylamines (5 mmol) in THF (10 mL) and the mixture was stirred for 1 hour at room temperature (RT). Then water (100 mL) was added to the reaction mixture, followed by stirring at RT for additional 24 hours. White seleninic acid (**3**) precipitated was filtered, washed with THF (3 x 30 mL) and dried in air. When hydrazine hydrate (2mmol, 0.2mL) was added to a solution of **3** (2mmol) in THF (10mL) and the mixture was stirred at RT for 24 hours followed by evaporation of THF to produce yellow to orange diselenide (**4**).



Scheme 1 5-selenization of salicylic acid derivates (see ref. 8 and 9 for **3a,4a,3c,3e,3f,3i**).

*2.2.1. Synthesis of 4-hydroxy-3-(methoxycarbonyl)benzeneseleninic acid (**3b**).*

Yield: 14%, mp: 136-138 °C, Found: C, 36.74; H, 3.02. Calc. for $C_8H_8O_5Se$: C, 36.52; H, 3.06%, δ_H 3.90(s, CH_3), 7.15(d, 3-H), 7.90(dd, 4-H), 8.21(d, 6-H), δ_C 52.62(CH_3), 113.84(C-1), 118.12(C-3), 128.29(C-6), 132.83(C-4), 139.34(C-5), 162.01(C-2), 168.10(C=O), δ_{Se} 1175, *m/z* (ESI) : 262.94616 (M^-. $C_8H_8O_5{}^{80}Se$ requires 262.94642).

*2.2.2. Synthesis of 4-hydroxy-3-(phenoxycarbonyl)benzeneseleninic acid (**3d**).*

Yield: 12%, mp: 140-1°C(decomp.), Found: C48.24, H3.09. Calc. for $C_{13}H_{10}O_5Se$: C48.02, H3.10%, δ_H 7.26(d, 3-H), 7.34(dd, 2',6'-2H), 7.38(d, 4'-H), 7.52(t, 3',5'-2H), 8.05(dd, 4-H), 8.46(d, 6-H), δ_C 114.10(C-1), 118.30(C-3), 121.91(2',6'-2C), 126.27(C-5), 129.08(4'-C), 129.65(3',5'-2C), 133.15(C-6), 139.31(1'-C), 150.13(C-4), 162.19(C-2), 165.55(C=O), δ_{Se} 1178, *m/z* (ESI) 324.96173 (M^-. $C_{13}H_{10}O_5{}^{80}Se$ requires 324.96207).

*2.2.3. Synthesis of 5,5'-diselanediyl-bis(2-hydroxybenzamide) (**4e**).*

Yield: 78%, mp: 288-90 °C, Found: C39.15, H2.75, N6.51. Calc. for $C_{14}H_{12}N_2O_4Se_2$: C39.09, H2.81, N6.51%, δ_H 6.86(d, 3-H), 7.55(dd, 4-H), 7.90(s, NH), 8.11(d, 6-H), 8.39(s, NH), 13.16(OH), δ_C 115.43(C-1), 118.67(C-3), 118.94(C-6), 134.12(C-4), 139.84(C-5), 161.65(C-2), 171.03(C=O), δ_{Se} 508, *m/z* (ESI) 430.90547 (M^-. $C_{14}H_{12}N_2O_4{}^{80}Se_2$ requires 430.90547).

*2.2.4. Synthesis of 2,2'-((5,5'-diselanediyl-bis(2-hydroxybenzoyl))-bis(azanediyl)) diacetic acid (**4f**).*

Yield: 72%, mp: 234-6°C(decomp.), Found: C39.35, H3.00, N5.23. Calc. for $C_{18}H_{16}N_2O_8Se_2$: C39.58, H2.95, N5.13%, δ_H 4.02(d, CH_2-2H), 6.94(d, 3-H), 7.57(dd, 4-H), 8.18(d, 6-H), 9.15(t, NH), δ_C 41.41(CH_2), 116.74(C-1), 118.88(C-3), 119.38(C-5), 134.44(C-6), 139.35(C-4), 160.00(C-2), 167.65(C=O), 171.09(COOH), δ_{Se} 507, *m/z* (ESI) 546.91483 (M^-. $C_{18}H_{16}N_2O_8{}^{80}Se_2$ requires 546.91483).

*2.2.5. Synthesis of 3-(2-hydroxy-5-seleninobenzamido)propanoic acid (**3g**).*

Yield: 32%, mp: 136-8°C(decomp.), Found: C37.24, H3.46, N4.41. Calc. for $C_{10}H_{11}NO_6Se$: C37.51, H3.46, N4.37%, δ_H 2.57(m, CH_2-2H), 3.52(m, CH_2-2H), 6.89(d, 3-H), 7.44(dd, 4-H), 8.09(d, 6-H), 8.92(t, NH), δ_C 33.55(CH_2), 35.38(CH_2), 116.81(C-1), 118.95(C-3), 119.16(C-5), 133.24(C-6), 138.51(C-4), 159.35(C-2), 167.67(C=O), 172.98(COOH), δ_{Se} 1176, *m/z* (ESI) 319.98875 (M^-. $C_{10}H_{11}NO_6{}^{80}Se$ requires 319.96788).

*2.2.6. Synthesis of 3,3'-((5,5'-diselanediyl-bis(2-hydroxybenzoyl))-bis(azanediyl)) dipropanoic acid (**4g**).*

Yield: 75%, mp: 250-2°C(decomp.), Found: C41.60, H3.43, N4.79. Calc. for $C_{20}H_{20}N_2O_8Se_2$: C41.83, H3.51, N4.88%, δ_H 2.42(t, CH_2-2H), 3.51(m, CH_2-2H), 6.85(d, 3-H), 7.44(dd, 4-H), 8.08(d, 6-H), 9.56(s, NH), δ_C 33.88(CH_2), 35.91(CH_2), 116.40(C-1), 118.22(C-5), 119.58(C-3), 135.46(C-6), 138.74(C-4), 162.54(C-2), 166.62(C=O), 175.10(COOH), δ_{Se} 515, *m/z* (ESI) 574.94623 (M^-. $C_{20}H_{20}N_2O_8{}^{80}Se_2$ requires 575.01249).

*2.2.7. Synthesis of 5-(2-hydroxy-5-seleninobenzamido)pentanoic acid (**3h**).*

Yield: 59%, mp: 130-2°C(decomp.), Found: C41.23, H4.47, N4.05. Calc. for $C_{12}H_{15}NO_6Se$: C41.39, H4.34, N4.01%, δ_H 1.57(m, CH_2-4H), 2.27(t, CH_2-2H), 3.33(m, CH_2-2H), 7.11(d, 3-H), 7.84(dd, 4-H), 8.33(d, 6-H), 9.04(t, NH), δ_C 22.08(CH_2), 28.38(CH_2), 33.39(CH_2), 38.94(CH_2), 115.95(C-1), 118.18(C-3), 126.51(C-6), 130.98(C-4), 138.52(C-5), 162.62(C-2), 167.94(C=O), 174.53(COOH), δ_{Se} 1177, *m/z* (ESI) 347.99946 (M^-. $C_{12}H_{15}NO_6{}^{80}Se$ requires 347.99918).

*2.2.8. Synthesis of 5,5'-((5,5'-diselanediyl-bis(2-hydroxybenzoyl))-bis(azanediyl)) dipentanoic acid (**4h**).*

Yield: 75%, mp: 255-7°C(decomp.), Found: C45.86, H4.37, N4.56. Calc. for $C_{24}H_{28}N_2O_8Se_2$: C45.73, H4.48, N4.44%, δ_H 1.56(s, CH_2-4H), 2.20(s, CH_2-2H), 3.31(s, CH_2-2H), 6.81(d, 3-H), 7.42(dd, 4-H), 8.10(d, 6-H), 9.60(s, NH), δ_C 22.87(CH_2), 28.98(CH_2), 35.13(CH_2), 38.69(CH_2), 116.19(C-1), 117.93(C-5), 119.72(C-3), 135.30(C-6), 138.94(C-4), 163.30(C-2), 167.18(C=O), 176.21(COOH), δ_{Se} 517, *m/z* (ESI) 631.00879 (M^-. $C_{24}H_{28}N_2O_8{}^{80}Se_2$ requires 631.10314).

*2.2.9. Synthesis of 6,6'-((5,5'-diselanediyl-bis(2-hydroxybenzoyl))-bis(azanediyl)) dihexanoic acid (**4i**).*

Yield: 83%, mp: 233-5°C(decomp.), Found: C47.17, H4.85, N3.98. Calc. for $C_{26}H_{32}N_2O_8Se_2$: C47.43, H4.90, N4.25%, δ_H 1.29(m, CH_2-2H), 1.52(m, CH_2-4H), 2.20(t, CH_2-2H), 3.25(m, CH_2-2H), 6.86(d, 3-H), 7.53(dd, 4-H), 8.09(d, 6-H), 8.80(t, NH), 12.91(s, COOH), δ_C 24.29(CH_2), 26.09(CH_2), 28.55(CH_2), 33.67(CH_2), 38.92(CH_2), 116.16(C-1), 118.80(C-3), 118.85(C-5), 133.71(C-6), 139.36(C-4), 160.84(C-2), 167.97(C=O), 174.48(COOH), δ_{Se} 509, *m/z* (ESI) 659.04173 (M^-. $C_{26}H_{32}N_2O_8{}^{80}Se_2$ requires 659.04163).

*2.2.10. Synthesis of 4-hydroxy-3-(propylcarbamoyl)benzeneseleninic acid (**3j**).*

Yield: 63%, mp: 117-8°C(decomp.), Found: C41.41, H4.52, N4.90. Calc. for $C_{10}H_{13}NO_4Se$: C41.39, H4.52, N4.83%, δ_H 0.90(t, CH_3-3H), 1.57(m, CH_2-2H), 3.27(m, CH_2-2H), 7.11(d, 3-H), 7.84(dd, 4-H), 8.34(d, 6-H), 9.04(t, NH), δ_C 11.38(CH_3), 22.06(CH_2), 40.85(CH_2), 115.84(C-1), 118.05(C-3), 126.41(C-6), 130.84(C-4), 138.45(C-5), 162.55(C-2), 167.98(C=O), δ_{Se} 1178, *m/z* (ESI) 289.99401 (M^-. $C_{10}H_{13}NO_4{}^{80}Se$ requires 289.99370).

*2.2.11. Synthesis of 5,5'-diselanediyl-bis(2-hydroxy-N-propylbenzamide) (**4j**).*

Yield: 85%, mp: 247-8°C, Found: C46.86, H4.67, N5.50. Calc. for $C_{20}H_{24}N_2O_4Se_2$: C46.70, H4.70, N5.45%, δ_H 0.90(t, CH_3-3H), 1.56(m, CH_2-2H), 3.26(m, CH_2-2H), 6.89(d, 3-H), 7.56(dd, 4-H), 8.12(d, 6-H), 8.83(t, NH) 12.96(s, OH), δ_C 11.35(CH_3), 22.02(CH_2), 40.80(CH_2), 116.05(C-1), 118.73(C-3, C-5), 133.66(C-6), 139.35(C-4), 160.80(C-2), 167.95(C=O), δ_{Se} 511, *m/z* (ESI) 514.99784 (M^-. $C_{20}H_{24}N_2O_4{}^{80}Se_2$ requires 515.02898).

*2.2.12. Synthesis of 3-(butylcarbamoyl)-4-hydroxybenzeneseleninic acid (**3k**).*

Yield: 73%, mp: 128-30°C(decomp.), Found: C43.56, H4.87, N4.41. Calc. for $C_{11}H_{15}NO_4Se$: C43.43, H4.97, N4.60%, δ_H 0.90(t, CH_3-3H), 1.33(m, CH_2-2H), 1.53(m, CH_2-2H), 3.30(m, CH_2-2H), 7.10(d, 3-H), 7.83(dd, 4-H), 8.32(d, 6-H), 8.99(t, NH), δ_C 13.74(CH_3), 19.74(CH_2), 30.98(CH_2), 38.91(CH_2), 116.06(C-1), 118.19(C-3), 126.57(C-6), 130.94(C-4), 138.51(C-5), 162.58(C-2), 167.89(C=O), δ_{Se} 1177, *m/z* (ESI) 304.00955 (M^-. $C_{11}H_{15}NO_4{}^{80}Se$ requires 304.00935).

*2.2.13. Synthesis of 5,5'-diselanediyl-bis(N-butyl-2-hydroxybenzamide) (**4k**).*

Yield: 79%, mp: 245-7°C, Found: C48.80, H5.28, N5.08. Calc. for $C_{22}H_{28}N_2O_4Se_2$: C48.72, H5.20, N5.16%, δ_H 0.91(t, CH_3-3H), 1.33(m, CH_2-2H), 1.53(m, CH_2-2H), 3.29(m, CH_2-2H), 6.89(d, 3-H), 7.56(dd, 4-H), 8.12(d, 6-H), 8.82(t, NH), 12.97(s, OH), δ_C 13.56(CH_3), 19.58(CH_2), 30.76(CH_2), 38.68(CH_2), 115.96(C-1), 118.65(C-5), 118.72(C-3), 133.58(C-6), 139.31(C-4), 160.80(C-2), 167.89(C=O), δ_{Se} 510, *m/z* (ESI) 543.02919 (M^-. $C_{22}H_{28}N_2O_4{}^{80}Se_2$ requires 543.11197).

*2.2.14. Synthesis of 3-(hexylcarbamoyl)-4-hydroxybenzeneseleninic acid (**3l**).*

Yield: 43%, mp: 136-8°C(decomp.), Found: C47.10, H5.76, N4.20. Calc. for $C_{13}H_{19}NO_4Se$: C46.99, H5.76, N4.22%, δ_H 0.85(t, CH_3-3H), 1.28(m, CH_2-6H), 1.52(m, CH_2-2H), 3.29(m, CH_2-2H), 6.87(d, 3-H), 7.44(dd, 4-H), 8.11(d, 6-H), 8.83(t, NH), δ_C 13.84(CH_3), 22.02(CH_2), 26.11(CH_2), 28.70(CH_2), 30.94(CH_2), 38.91(CH_2), 116.39(C-1), 118.86(C-3), 118.89(C-5), 132.67(C-6), 138.37(C-4),159.82(C-2), 167.94(C=O), δ_{Se} 1177, *m/z* (ESI) 332.04105 (M^-. $C_{13}H_{19}NO_4{}^{80}Se$ requires 332.04065).

*2.2.15. Synthesis of 5,5'-diselanediyl-bis(N-hexyl-2-hydroxybenzamide) (**4l**).*

Yield: 72%, mp: 212-4°C, Found: C52.27, H6.10, N4.81. Calc. for $C_{22}H_{28}N_2O_4Se_2$: C52.18, H6.06, N4.68%, δ_H 0.63(t, CH_3-3H), 1.07(m, CH_2-6H), 1.29(m, CH_2-2H), 3.05(m, CH_2-2H), 6.67(d, 3-H), 7.33(dd, 4-H), 7.88(d, 6-H), 8.58(t, NH) 12.52(s, OH), δ_C 13.83(CH_3), 22.00(CH_2), 26.09(CH_2), 28.76(CH_2), 30.92(CH_2), 39.02(CH_2), 116.08(C-1), 118.37(C-5), 118.75(C-3), 133.50(C-6), 139.26(C-4), 160.23(C-2), 167.83(C=O), δ_{Se} 509, *m/z* (ESI) 599.09155 (M^-. $C_{22}H_{28}N_2O_4{}^{80}Se_2$ requires 599.19677).

*2.2.16. Synthesis of 3-(heptylcarbamoyl)-4-hydroxybenzeneseleninic acid (**3m**).*

Yield: 11%, mp: 118-20°C(decomp.), Found: C48.48, H6.13, N4.08. Calc. for $C_{14}H_{21}NO_4Se$: C48.56, H6.11, N4.04%, δ_H 0.84(t, CH_3-3H), 1.27(m, CH_2-8H), 1.52(t, CH_2-2H), 3.27(m, CH_2-2H), 7.08(d, 3-H), 7.81(dd, 4-H), 8.30(d, 6-H), 9.02(t, NH), δ_C 13.93(CH_3), 22.05(CH_2), 26.40(CH_2), 28.39(CH_2), 28.73(CH_2), 31.32(CH_2), 38.97(CH_2),115.73(C-1), 118.01(C-3), 118.90(C-5), 126.30(C-6), 130.83(C-4), 162.51(C-2), 167.78(C=O), δ_{Se} 1176, *m/z* (ESI) 346.05566 (M^-. $C_{14}H_{21}NO_4{}^{80}Se$ requires 346.05630).

*2.2.17. Synthesis of 3-(cyclohexylcarbamoyl)-4-hydroxybenzeneseleninic acid (**3n**).*

Yield: 14%, mp: 133-5°C, Found: C47.21, H5.22, N4.27. Calc. for $C_{13}H_{17}NO_4Se$: C47.28, H5.19, N4.24%, δ_H 1.15(t, CH_2-H), 1.32(t, CH_2-2H), 1.38(d, CH_2-2H), 1.59(d, CH_2-H), 1.72(d, CH_2-2H), 1.82(d, CH_2-2H), 3.83(t, CH_2-H), 7.08(d, 3-H), 7.81(d, 4-H), 8.35(s, 6-H), 8.81(d, NH), δ_C 24.81(CH_2-2C), 25.20(CH_2), 32.08(CH_2-2C), 48.36(CH_2), 115.91(C-1), 118.03(C-3), 126.72(C-6), 130.74(C-4), 138.54(C-5), 162.55(C-2), 166.92(C=O), δ_{Se} 1177, *m/z* (ESI) 330.02421 (M^-. $C_{13}H_{17}NO_4{}^{80}Se$ requires 330.02500).

*2.2.18. Synthesis of 4-hydroxy-3-(phenylcarbamoyl)benzeneseleninic acid (**3o**).*

Yield: 17%, mp: 136-8°C(decomp.), Found: C48.23, H3.28, N4.39. Calc. for $C_{13}H_{11}NO_4Se$: C48.16, H3.42, N4.32%, δ_H 7.14(t, 4'-H), 7.18(d, 3-H), 7.37(t, 3',5'-2H), 7.71(d, 2',6'-2H), 7.85(dd, 4-H), 8.37(d, 6-H), 10.48(s, NH), 12.16(s, OH), δ_C 117.70(C-3), 119.04(C-1), 120.81(2',6'-2C), 124.23 (4'-C), 127.87(C-6), 128.76(3',5'-2C), 130.67(C-4), 138.14(C-5), 139.12(1'-C), 160.29(C-2), 165.04(C=O), δ_{Se} 1146 (KOH+D_2O), *m/z* (ESI) 323.97753 (M^-. $C_{13}H_{11}NO_4{}^{80}Se$ requires 323.97805).

*2.2.19. Synthesis of 5,5'-diselanediylbis(2-hydroxy-N-phenylbenzamide) (**4o**).*

Yield: 73%, mp: 242-4°C, Found: C53.65, H3.31, N4.73. Calc. for $C_{26}H_{20}N_2O_4Se_2$: C53.62, H3.46, N4.81%, δ_H 7.01(d, 3-H), 7.11(t, 4'-H), 7.33(t, 3',5'-2H), 7.61(dd, 4-H), 7.67(d, 2',6'-2H), 8.20(d, 6-H), 10.37(s, NH), 12.05(s, OH), δ_C 118.62(C-3), 119.14(C-5), 119.33(C-1), 120.96(2',6'-2C), 124.27(4'-C), 128.78(3',5'-2C), 134.70(C-6), 138.17(1'-C), 138.69(C-4), 158.69(C-2), 165.23(C=O), δ_{Se} 500, *m/z* (ESI) 582.96807 (M^-. $C_{26}H_{20}N_2O_4{}^{80}Se_2$ requires 582.96903).

2.3. GPx-like activity [8].

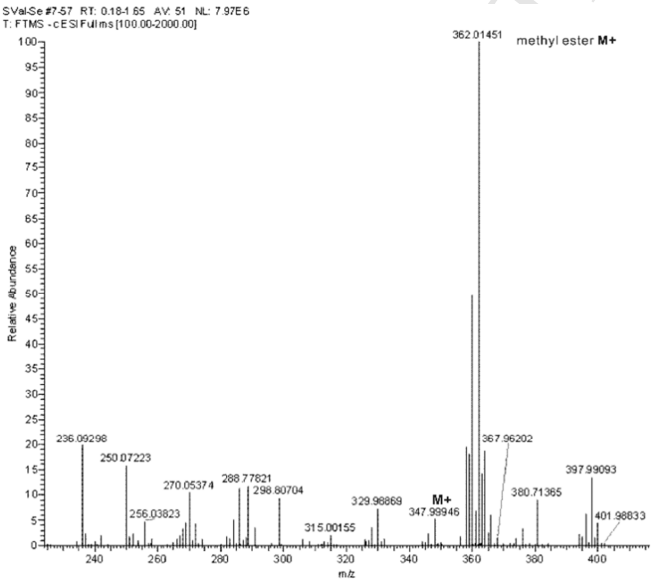
The catalytic reaction was run at 37 °C in a 1 mL reaction mixture consisting of 100 mM Tris-HCl buffer (pH 7.4) containing 5 mM EDTA and 0.1 % Triton X-100, 3 mM GSH, 0.2 mM NADPH, 1 U of glutathione reductase (GR) and 10 µM of the test compound (DMSO solution). The assay sample was equilibrated for 10 minutes in the absence of peroxide substrate and GPx-like reaction was initiated by addition of 0.5 mM *tert*-butyl hydroperoxide (*t*-BuOOH). The time-dependent decrease in absorbance at 340 nm (10 to 40 seconds after addition of *t*-BuOOH) was recorded. During the GPx-like reaction, reduced GSH is oxidized and the resulting disulfide (GSSG) is back-reduced by the GR reaction consuming stoichiometric amounts of NADPH. Since NADPH exhibits a local absorbance maximum (A_{cat}) at 340 nm but its oxidized counterpart (NADP) does not, NADPH oxidation can be quantified by measuring the decrease in absorbance at this wavelength. A blank assay (solvent control, A_{blank}) was run in the absence of catalysts. The rate of NADPH oxidation (υ_o) was calculated using a molar absorbance coefficient for NADPH of 6.22×10^3 $M^{-1} \cdot cm^{-1}$.

3. Results and discussion

3.1. Synthesis.

Under stirring at RT for 1h yellow 5-selenium trichlorides are formed, which are further hydrolyzed in water for 24 h to white 5-seleninic acids (**3**), followed by reduction by hydrazine hydrate at RT for 24 h to yellow diselenides (**4**).

In the previous study [9] we reported that the seleninic group of **3a** was methyl esterified during monocrystallization from methanol. Although we did not try to prepare any monocrystals of the new congeners **3**, their methyl esterification were identified from their HR-MS spectra with methanol as a solvent, for example as is seen for **3h** in Fig. 2. However, 5-seleninic acids of alkyl or phenyl salicylate esters did not show the possibility of methyl esterification (see Supplementary Data), the reason of which is unclear.



3.2. GPx-like activity.

GPx-like activities of new 5-seleninic acids were assayed in coupled reductase model [9] with glutathione and *tert*-butyl hydroperoxide (*t*-BuOOH) as substrates. Most of the 5-seleninic acids (**3a**, **3b**, **3d-3h, 3j, 3k** and **3o**) showed higher GPx-like activities than ebselen (Table 1) and when normalized to selenium content, the diselenides (**4e**-**4k** and **4o**) also exerted almost equivalent GPx-like activities to their corresponding precursors, 5-seleninic acids **3** (data not shown). Surprisingly, like in **3i** [9], there were no detectable GPx-like activities in **3l** and **3m**, where the number of carbon atoms comprising the side chain bonded to the nitrogen of salicyloylamine moiety exceeded more than 6, and so was it in **3n**, which carries a cyclohexyl ring instead of a normal chain bonded to the nitrogen of amide.

Table 1 The rate of NADPH oxidation (υ_0) in the presence of compounds **3** (10 µM) and their GPx-like activities relative to ebselen (n =3).

compound	ClogP	υ_0 (µM min^{-1})	Relative Activity (RA)
Ebselen		5.19 ± 0.51	1
3a	0.18	16.40 ± 1.02	2.8
3b	0.32	8.97 ± 0.85	1.7
3c	0.85	5.21 ± 0.28	0.9
3d	1.83	9.54 ± 0.82	1.9
3e	-0.72	12.05 ± 1.82	2.1
3f	-0.72	6.48 ± 0.47	1.1
3g	-0.66	8.92 ± 0.45	1.7
3h	-0.35	9.44 ± 0.42	1.8
3i	0.17	no detectable	0
3j	0.53	12.28 ± 1.12	2.4
3k	1.06	6.67 ± 0.46	1.3
3l	2.12	no detectable	0
3m	2.65	no detectable	0
3n	1.50	no detectable	0
3o	1.26	6.14 ± 0.51	1.1

3.3. Hydrophobic effect on GPx-like activity.

To get further more meaningful understanding of these lacks of GPx-like activity, logPs related to molecular hydrophobicity were calculated (ClogP) with the use of ChemBioDraw 2010 to correlate them with GPx-like activities relative to that of ebselen. This software was selected because of its superiority to other commercially available chemical softwares including ACD/log P and HyperChem [10].

In *N*-salicyloyl ω-carboxy-*n*-alkylamines (**3f**-**3i**), the chain lengths and ClogPs are in proportion to GPX-like activities from

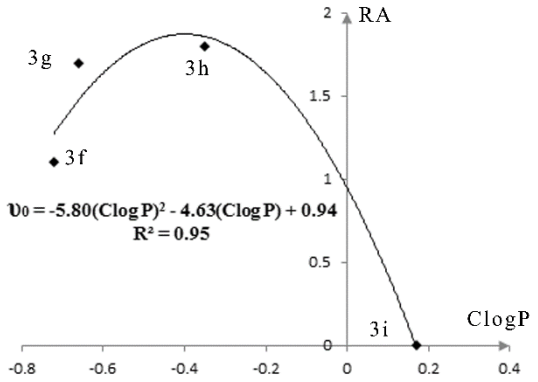
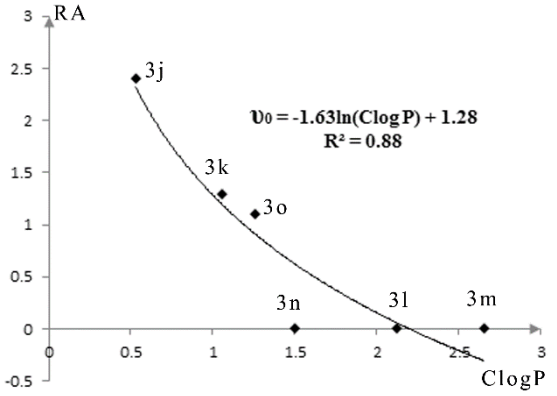


Fig. 3 Plot of ClogPs and relative GPx-like activities of 5-seleninic acids of *N*-salicyloyl ω-carboxyalkylamines.

3f [8] to **3g**, but as the number of carbon atoms of a side chain increases from 5 to 6 (from **3h** to **3i** [9]), the increment of ClogP gets much more (*Δ*ClogP = 0.52) than ever (from 2 to 3: *Δ*ClogP = 0.06 and from 3 to 5: *Δ*ClogP = 0.31) and, moreover, GPx-like activity does not decrease but gets disappeared. We have, therefore, plotted using Microsoft Excel the relative GPx-like activities and ClogPs (Fig. 3), which resulted in satisfactory quantitative relationship (R^2=0.95). From the inversed parabolic equation obtained (Fig. 3) we could get the maximum relative GPx-like activity (1.87) corresponding to the ClogP (-0.39). According to the above equation, ClogP of the compound whose substituent R is aminobutyric acid in Scheme 1 is -0.30 and its GPx-like activity is calculated to be 1.82, which suggests that this congener could be one of the optimal derivatives in this series.

On the contrary to the above series, in *N*-salicyloyl *n*-alkyl amines (**3j**-**3m**), as the alkyl chain gets elongated from *n*-propyl (**3j**) to *n*-butyl (**3k**), GPx-like activity gets lowered with the



increase of ClogP. Interestingly, also in this series, as the number of chain carbon atoms gets 6 (**3l**) or 7 (**3m**), GPx-like activity is not detectable. A cyclohexyl derivative (**3n**) with ClogP (1.51) between those of *n*-butyl derivative (**3k**) and *n*-hexyl one (**3l**), exerts no GPx-like activity, too. We have also obtained the quantitative relation equation (R^2=0.88) for this series. From the graph of the equation (Fig. 4) one could realize that there would exist a switching threshold of ClogP

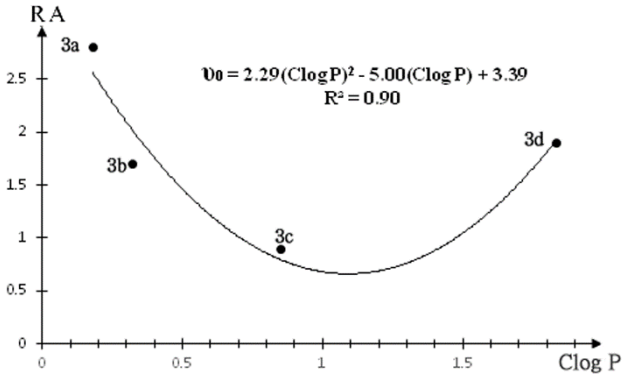


Fig. 6 Plot of ClogPs and relative GPx-like activities of 5-selenino salicylic acid and its esters

(about 2.20) for GPx-like activity. GPx-like activity of a phenyl derivative (**3o**) similar to ebselen could be assigned to its ClogP (1.27) which is beyond the threshold. Furthermore, although we did not synthesize *n*-methyl and ethyl homologues (Fig. 5) in this series, it could be expected that they might exert 6.48 and 4.31 times higher GPx-like activity than ebselen, for their ClogP values are -0.522 and -0.007, which are far lower than the threshold.

In addition, we have obtained a satisfactory quantitative relationship (R^2=0.91) between ClogPs and GPx-like activity for 5-selenino salicylic acid and its esters (Fig 6).

From these results, we could suggest that activities of a series of organoselenium GPx mimics might have a quantitative relationship with their ClogPs, which could be useful in designing better analogues or homologues in each series. This concept would be connected with the suggestion [11] that molecular hydrophobicity could improve cellular uptake of GPx mimics.

3.4. Relationship between ClogPs and catalytic activities of known aromatic selenium GPx mimics.

A number of reports have been published on development of improved GPx mimics, where the explanations [12] were focused mainly on structural novelty or superiority of newer structures to older ones, but there have been only a few researches [13] on structure-activity relationships in one series, for example, the QSAR study of aromatic organochalcogens with relation to their molecular orbital energies (LUMO and electrochemical oxidation potential) and atomic electron densities, preference of steric effect to electronic one in *ortho*-substitution of ebselen, electronic contribution of substituents (Hammett plot) in cyclic seleninates and spirodioxyselenuranes, etc. We have, therefore, tried to delineate GPx-like activities of some known aromatic selenium derivatives with respect to their ClogPs in each series.

Fig. 2 HR-MS spectrum of **3h** in MeOH.

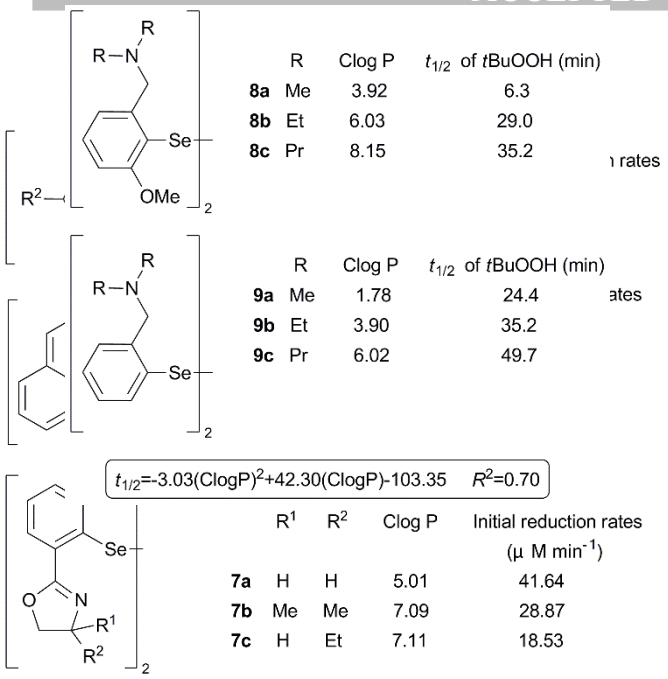


Fig. 7 ClogPs and peroxidase activities of some aromatic diselenides.

Most of known aromatic selenium GPx mimics are diaryl diselenides and ebselen derivatives. Mugesh et al. [14] reported thiol peroxidase-like activities of some aromatic diselenides, which might be grouped into alkyl-substituted diphenyl diselenides, dinaphtyl diselenides and 4,5-dihydrooxazol substituted diphenyl diselenides (Fig. 7). In the case of diphenyl diselenides, inactivity of *p-tert*-butyl-*o,o'*-dimethyl substituted derivative (**5b**) can be explained in some measure on the point of ClogP. That is, because ClogP of **5b** (10.06) is much bigger than that of the non-substituted compound **5a** (4.41, υ_0= 24.08μM min^{-1}), **5b** could not exert activity. In dinaphtyl diselenides (**6a**-**6c**), peroxidase activities are in quite a quantitative inverse proportion (R^2=0.99) to ClogPs. Such a trend can be seen also in 4,5-dihydrooxazol substituted diphenyl diselenides **(7a**-**7c**), but if we consider the fact that alkyl substituted derivatives (**7b** and **7c**) were actually inactive in lower concentration [14], we could suggest that their excessive hydrophobicity compared to that of unsubstituted one (**7a**) might lead to their inactivity.

Mugesh and Bhabak [15] suggested 6-methoxylation (*o*-methoxylation) as a means for enhancement of GPx-like activities of diselenides of *N, N*-dialkylbenzylamines. Altogether, there exists a parabolic relationship between ClogP and half-life of *t*-BuOOH (Fig. 8), and the correlation coefficient is 0.70, which is relatively satisfied. Considering the authors' explanation, however, that the stabilization of selenium atom by 6-methoxylation could be responsible for higher activities of **8** than those of **9**, we could sugget that it would be better to add electonic effect instead of steric one to hydrophobic effect to obtain more reliable relationship equation.

Fig. 4 Plot of ClogPs and relative GPx-like activities of 5-seleninic acids of *N*-salicyloyl alkyl or phenyl amines.

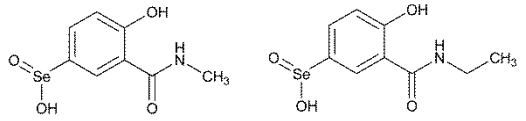
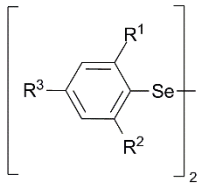


Fig. 5 The congeners estimated to exert higher GPx-like activity.

Wirth [16] measured GPx-like activities of some oxygen-containing diselenides (Fig. 9) using GR coupled assay with either hydrogen peroxide (H_2O_2) or *t*-BuOOH. He suggested that significantly lower activity of bis-*ortho* substituted diselenides (**10b**-**10d**) could be attributed to steric hindrance, but actually **10c** showed much lower activity than **10d**, though its substituent was less bulkier than that of **10d**, for which he mentioned a decrease of electron density at selenium atom by electron withdrawing substituent CF_3 of **10c**. However, ClogP of CF_3 substitued compoud **10c** is bigger than that of 1'-hydroxypropyl substitued one **10d.** The inferior activity of **10c** to the others could be responsible for its lowest ClogP, as shown in Fig. 9. About 2 fold discrepancy in GPx-like activity between hydroxyl substituted **10a** and methoxy substituted **10e** has not been tried to explain before, but higher hydrophobicity of **10e** might be attributed to its less activity. ClogPs and GPx-like activities in this diselenide series are in inverse parabolic relation (R^2=0.87 for H_2O_2 and R^2=0.85 for *t*-BuOOH), which reveals that there might exist a ClogP for maximal GPx-like activity. The optimum ClogPs from the above equations are 4.42 and 4.43, when their GPx-like activities would be 27.25 μM min^{-1} and 15.74 μM min^{-1} for H_2O_2 and *t*-BuOOH, respectively. There might be exemplified compounds with ClogPs close to the above optimal ones (Fig 10). For bis-(2-methyl-4-methoxy-6-hydroxypheny) diselenide, the calculated activities are 27.04μM min^{-1} for H_2O_2 and 10.67μM min^{-1} for *t*-BuOOH from its ClogP (4.27), and for bis-(2-amino-



	R^1	R^2	R^3	Clog P	reduction rate of NADPH (nmol of NADPH min^{-1})	
					H_2O_2	*t*-BuOOH
10a	-CH(OH)Et	H	H	4.01	26.6	13.9
10b	-CH(OH)Et	Me	H	5.01	20.2	13.0
10c	-CH(OH)Et	CF_3	H	5.78	8.7	4.7
10d	-CH(OH)Et	-CH(OH)Et	H	3.61	18.8	9.5
10e	-CH(OMe)Et	H	H	5.68	14.5	7.8
10f	$-CH_2CH(OH)Et$	H	H	3.41	17.9	11.5
10g	H	H	OMe	4.25	30.2	17.7

H_2O_2: V_0= -9.58(Clog P)^2 + 84.69Clog P) - 159.90 R^2 = 0.87
t-BuOOH: V_0= -5.69(Clog P)^2 + 50.44(Clog P) - 95.97 R^2 = 0.85

Fig. 9 ClogPs and GPx-like activities of oxygen-containing diphenyl diselenides.

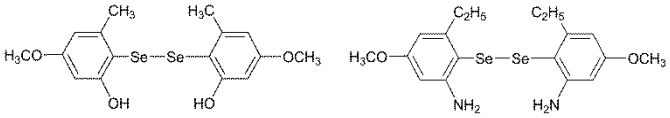
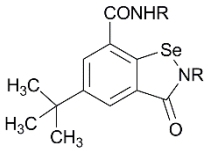


Fig. 10 Bis-(2,4,6-substituted phenyl)-diselenides with close to optimal ClogPs.

4-methoxy-6-hydroxyphenyl) diselenide, they are 26.74μM min^{-1}, 174.39μM min^{-1} and 174.20μM min^{-1}, respectively, from their ClogPs (2.47, 2.48 and 2.44, respectively).



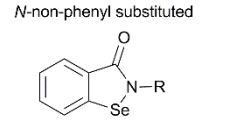
	R	Clog P	Consumption rate of NADPH (μ M min^{-1})
11a	Me	2.50	15.71
11b	*i*Pr	4.18	7.06
11c	Ph	6.04	1.84

v_0=-3.91(ClogP)+24.76 R^2=0.97

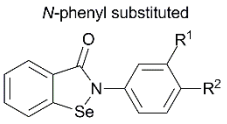
Fig. 11 ClogPs and GPx-like activities of *p-tert*-butyl-*o*-(*N*-alkyl/phenyl) carbamoyl ebselen derivatives.

ClogP can also be applied to some ebselen derivatives. Zade et al. [17] published a report on the synthesis and GPx-like activities of *p-tert*-butyl-*o*-(*N*-alkyl/phenyl) carbamoyl ebselen derivatives (**11**), when they indicated that the lower activity of **11c** relative to that of ebselen could be attributed to its poor solubility, which could be due to its higher hydrophobicity (ClogP = 6.04 in Fig. 11). There was a pronounced reciprocal proportional relation (R^2=0.97) between ClogP values and GPx-like activities.

Mugesh and Bhabak [18] suggested that phenyl substituents on the nitrogen atom were important for the GPx-like activity of ebselen, but in fact, their experimental results presented that non-*N*-phenyl substituted analogues (**12a**-**12c** in Fig. 12) showed higher or much higher activity than *p*-bromophenyl substituted one (**12g**). From the lower half of Fig. 12 one could note that **12g** with the largest ClogP shows the lowest GPx-like activity among *N*-phenyl derivatives tested, when there exists a significant parabolic relation (R^2=0.77)



	R	Clog P	Initial reduction rates (*t*-BuOOH), (μ M min^{-1})
12a	H	1.08	59.0
12b	CH_2CH_2OH	1.16	124.2
12c	$CSNH_2$	2.30	216.1



	R^1	R^2		
12d	H	H	3.70	86.1
12e	OH	H	3.04	142.6
12f	H	OH	3.04	169.1
12g	H	Br	4.57	29.8

v_0=-39.29(ClogP)^2-196.86(ClogP)-73.76 R^2=0.77

Fig. 12 ClogPs and GPx-like activities of *N*-substituted ebselen derivatives.

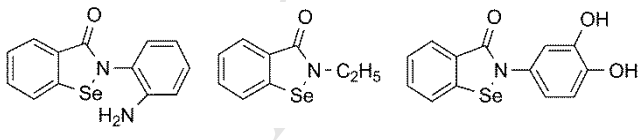
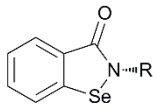
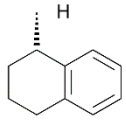
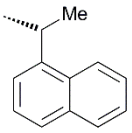
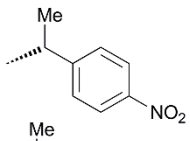
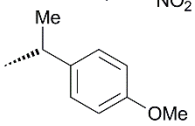
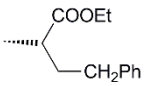
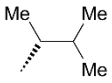
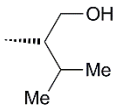
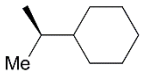
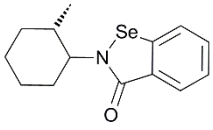


Fig. 13 *N*-substituted ebselen derivatives with close to optimal ClogPs.

between GPx-like activities and ClogPs in *N*-phenyl and non-phenyl derivatives. The obtained equation reveals that ClogP might have an optimal value (2.52) for maximal GPx-like activity (174.46μM min^{-1}), and we have estimated the following compounds with ClogPs close to the above optimal one (Fig 13). The estimated activities of 2-aminophenyl, ethyl and 3,4-dihydroxyphenyl substituents are 174.36μM min^{-1},

Elsherbini et al. [19] have recently synthesized several chiral ebselen analogues as GPx-like mimics (Fig. 14), where they indicated that the highest activity of **13g** was due to its higher solubility in the reaction medium compared to the other compounds. As can be seen from Fig. 14, **13g** has the

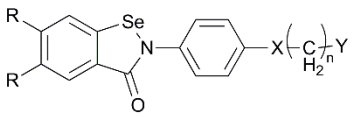


	R	Clog P	Initial rate (GSH/GSSG assay) (μ M min^{-1})	
			H_2O_2	CumOOH
12d	H	3.70	111.3	36.7
13a		4.70	28.1	1.0
13b		5.21	13.2	3.4
13c		3.78	52.7	12.1
13d		3.96	34.7	9.4
13e		4.03	38.7	6.7
13f		3.73	126.5	28.4
13g		2.40	164.2	71.0
13h		4.92	33.9	13.7
13i		5.03	27.7	3.4

v_0=-85.79ln(ClogP)+138.75 R^2=0.80 (H_2O_2)
v_0=-198.40ln(ClogP)+340.97 R^2=0.76 (CumOOH)

Fig. 14 ClogPs and GPx-like activities of ebselen and its chiral analogues.

smallest ClogP among the compounds tested, which could be regarded as another reasonable delineation of its highest GPx-like activity. They also explained that steric hindrance in **13i** could be the cause of its lower GPx-like activity in both assays with GSH and PhSH as the substrate. Here we can make an additional remark that the higher ClogP of **13i** (5.06) could



	R	X	n	Y*	Clog P	Initial rate (μ M min^{-1})
14a	H	CH_2	0	pp	4.73	166.1
14b	H	CH_2	1	pr	4.48	115.1
14c	H	O	2	pp	4.96	100.1
14d	OMe	CH_2	0	pr	3.83	115.1
14e	OMe	CH_2	0	pp	4.39	149.0
14f	OMe	CH_2	0	-N(Me)CH_2Ph	5.29	59.87
14g	OMe	CH_2	1	pr	8.85	112.8
14h	OMe	CH_2	1	pp	4.70	121.3
14i	OMe	O	2	pp	4.61	122.7
14j	OMe	O	3	pp	4.92	113.7
14k	OMe	O	4	pp	5.03	85.85

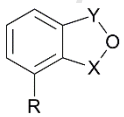
*pp:piperidinyl  pr:pyrrole 

V_0 = -93.24(Clog P)^2 + 818.48(Clog P)- 1660.60 R^2 = 0.63

Fig. 15 ClogPs and GPx-like activities of ebselen derivatives inhibiting acetylcholine esterase.

account for its lower activity. In GSH/GSSG assay ClogP values are found to be in comparably reliable inverse proportion to GPx-like activities (R^2=0.80 for H_2O_2 and R^2=0.76 for CumOOH).

Luo et al. [20] consulted the structures of ebselen and donepezil to design and synthesize a new series of ebselen derivatives (**14**) as hybrids of GPx mimics and cholinesterase inhibitors against Alzheimer's disease. As is seen in Fig. 15, the relationship between ClogP and GPx-like activity in 11 derivatives follows inverse parabolic function (R^2=0.63) which means that there could also exist a ClogP for maximal activity in this series like in **3**, but the low correlation coefficient, R^2 highlights the additional contributions of other structural factors on GPx-like activity to be further considered.



	R	X	Y	Clog P	Initial rate (μ M min^{-1})
15a	H	Se=O	CH_2	0.67	467
15b	NO_2	Se=O	C=O	-0.12	816
15c	NO_2	Se	C=O	2.11	731
15d	NO_2	Se	CH_2	1.77	265
15e	NO_2	Se=O	CH_2	0.41	565
15f	NO_2	Se	CHOH	0.58	342

V_0 = 356.27(Clog P)^2 - 818.22(Clog P)+762.27 R^2 = 0.73

Cyclic seleninate/selenenate ester is well known to be a lead of successful GPx mimics. Singh et al. [21] reported that *o*-nitro could stabilise aromatic cyclic selenenate/seleninate esters to exert higher GPx-like activities in comparison to that of the analogue without *o*-nitro group (Fig. 16). Although the introduction of *o*-nitro group enhanced the GPx-like activity, but the increment was found to be not so great from the comparison of **15a** and **15e**, and instead, electronic effects of polar S=O and C=O groups were more significant (**15d** and **15e**, **15c** and **15d**), which was, of course, mentioned by authors. These polar groups could directly be reflected to molecular hydrophobicity. Indeed, GPx-like activities of these aromatic cyclic selenenate/seleninate esters were in relatively good relationship to ClogPs (R^2=0.73). The parabolic graph obtained reveals that such aromatic cyclic selenenate/seleninate esters might certainly exert at least superior GPx-like activity to ebselen.

4. Conclusions

We have synthesized 19 new 5-seleninic acids and some of their diselenides of methyl or phenyl salicylates, *N*-salicyloyl ω-carboxyalkylamines, or *N*-salicyloyl alkyl or phenyl amines, and measured GPx-like activities of the 5-seleninic acids with coulpled reductase assay. Structure-activity relationship study using ClogP reflecting hydrophobic property of the mimics has concluded that in each series observed there could exist its own relationship between ClogPs and GPx-like activities of the congeners and that it could have a switching threshold of ClogP for the activity or its limited maximal activity. Not only ClogP could, of course, account for the absence of GPx-like activity of some derivatives, which should be further elucidated in other ways. Applications of ClogP correlation to diverse aromatic selenium GPx mimics including diaryl diselenides and ebselen derivatives also showed some meaningful or quantitative relationships between ClogPs and GPx-like activities in each series. The series with R^2 lower than 0.9 are thought to be further explored for other structural factors on GPx-like activity. In addition, it should be pointed out that the source of thiols could be significant for QSAR of GPx mimics, because benzene thiol (PhSH) or benzyl thiol (BnSH) might bring about confusion in QSAR analysis due to their thiol exchange effect. In fact, we could not succeed in relating ClogPs with GPx-like activities for data of many GPx mimics with PhSH or BnSH as thiol source. Our results did not cover aliphatic selenium GPx mimics, but were focused on aromatic ones, which constituted majority of GPx mimics reported until now. As in drug design field, further more extensive QSAR studies are required for each series of not only aromatic but also aliphatic selenium/tellurium GPx mimics to get successive druggable GPx mimic candidates.

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Appendix A. Supplementary data

Supplementary data related to this article can be found in the online version at http://dx.doi.org/xx.xxxx/j.jorganchem.201x.xx.xxx.

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Fig. 16 ClogPs and GPx-like activities of aromatic cyclic seleninate and selenenate esters.

Highlight

- Synthesis and determination of GPx-like activity of 19 new compounds.
- Quantitative relationships between hydrophobicity (ClogP) and GPx-like activity of several 5-seleninic acids.
- Applying the relationship to the known GPx-mimics (aromatic diselenides, ebselen derivatives, etc.).