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Synthesis, characterization, structures and GPx mimicking activity of pyridyl and pyrimidyl based organoselenium compounds

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ABSTRACT

Pyridyl and pyrimidyl based organoselenium compounds have been synthesized and characterized by analytical and spectroscopic techniques. Molecular structures of 2,2′-dipyrimidyl diselenide (**1b**), 2,2′-dipyrimidyl selenide (**2b**) and 2-pyrimidyl seleno ethanoic acid (**3d**) have been determined by single crystal X-ray diffraction analyses. The **3d** is associated in the solid state through hydrogen bonding between carboxylic acid proton and N2 of the pyrimidyl ring of an adjacent molecule. The *in vitro* GPx-like catalytic activity for these compounds was evaluated by ^{1}H NMR and HPLC methods where H_2O_2 was reduced by dithiothreitol (DTT^{red}) and glutathione (GSH) as a thiol cofactor, respectively, in the presence of catalytic amounts of organoselenium compounds. The electron density around selenium atom (−SeSe− or −Se−) which is reflected by ^{77}Se{^{1}H} NMR chemical shifts, has been found to be one of the crucial factors in influencing their overall GPx like activity.

1. Introduction

The chemistry of organoselenium compounds is making great strides in diverse areas ranging from organic synthesis [1–3], coordination chemistry [4–6], materials science [7–9], pharmacy [10,11] and biology [12–15]. Selenium is an essential micronutrient in biological system and is incorporated in the form of selenocysteine in several redox active enzymes. Glutathione peroxidase (GPx) is one of the important selenoenzymes which in conjunction with its thiol cofactor glutathione (GSH) catalyses reduction of several peroxides. Considerable efforts have been made to develop antioxidant for their applications in treating oxidative stress related diseases. The GPx mimicking activity was first reported in a synthetic organoselenium compound, 2-phenyl-1,2-benzoisoselenazol-3-(2H)-one (ebselen) [16,17] and its mechanistic aspects have also been reported [18]. This led to the design and development of several organoselenium compounds having different types of bonding and non-bonding interaction between selenium and nearby heteroatom, '*X*' (*X* = N or O) as GPx mimics [14]. The following empirical design features have been recognized in GPx active organoselenium compounds.

- Organoselenium compounds, both mono- and di-selenides, containing alkyl groups with OH, NH_2, COOH functionality at terminal position are active [19–22].
- Diselenides are more active than the corresponding monoselenides [23].
- Diselenides which show weak secondary intramolecular Se···*X* (*X* = O or N) interactions, in general, show good activity [24–28].
- Diselenides containing heterocyclic ring (*e.g.*, pyridine, quinoline) are better catalysts than the compounds containing simple aryl groups (*e.g.*, Ph_2Se_2) [29].

We have recently incorporated these design features in nicotinamide based organoselenium compounds. One of these derivatives, nocotinamide diselnide [2-NC_5H_3(3-$CONH_2$)Se]$_2$, exhibited good GPx activity *in vitro* [30]. This has prompted us to design molecules incorporating above empirical features. Accordingly, we have examined organoselenium compounds containing N-heterocyclic, 2-pyridyl and 2-pyrimidyl, rings and evaluated their GPx mimicking activity. The results of this work are reported herein.

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2. Experimental

2.1. Materials and methods

Elemental selenium (99.99%), sodium borohydride, bromoacetic acid, 3-bromopropionic acid, 4-bromobutyric acid, 2-bromoethylamine hydrobromide, 3-chloropropylamine hydrochloride, 2-bromoethanol, 3-bromopropanol and diphenyl diselenide were purchased from commercial sources (Aldrich/Fluka). All reactions were carried out under a nitrogen atmosphere. Solvents were purified and distilled prior to use. The compounds were purified by column chromatography on silica gel 60/120 mesh size. Melting points were determined in capillary tubes and are uncorrected. Elemental analyses were carried out on Flash EA 1112 Series CHNS Analyzer. NMR spectra were recorded on a Bruker Avance-II 300 MHz spectrometer operating at 300.13 (^{1}H), 75.47 (^{13}C{^{1}H}) and 57.25 (^{77}Se{^{1}H}) MHz. ^{1}H and ^{13}C{^{1}H} NMR chemical shifts were relative to internal chloroform peak (δ = 7.26 ppm for ^{1}H and δ = 77.0 for ^{13}C{^{1}H} NMR). The ^{77}Se{^{1}H} NMR chemical shifts were relative to external diphenyl diselenide (Ph_2Se_2) in $CDCl_3$ (δ 463.0 ppm relative to Me_2Se (0 ppm)). The mass spectra were recorded on an MS-500 Ion Trap (IT) Varian mass spectrometer at Sophisticated Analytical Instrumentation Facility (SAIF), Indian Institute of Technology-Bombay, Mumbai. The GPx like catalytic activities were evaluated on a Bruker Avance-II NMR spectrometer and JASCO HPLC detector model UV-2070.

2.2. Synthesis

2.2.1. Synthesis of py_2Se_2 (**1a**) and py_2Se (**2a**)

In a typical experiment, 2-bromopyridine (30 g, 189 mmol) was added to an aqueous brown solution of Na_2Se_2 (prepared from selenium powder (15 g, 190 mmol) in deoxygenated water and sodium borohydride (7.2 g, 189 mmol) at 0 °C under nitrogen. The reaction mixture was refluxed for 3 h till the solution became yellow containing a small amount of suspended selenium. The hot reaction mixture was filtered and allowed to cool to room temperature, whereupon dipyridyl diselenide (**1a**) (12.2 g, 42%) crystallized out as yellow crystals and was filtered using a Buchner funnel. The filtrate was extracted with chloroform (4 × 150 ml). The organic layer was dried over sodium sulfate and concentrated on rotavapor to yield a yellow sticky liquid which was purified by column chromatography (1:9, ethyl acetate:hexane) to give dipyridyl monoselenide (**2a**) (4.2 g, 19%) as a red oil.

py_2Se_2 (1a) m.p. 50–51 °C (lit 47.5–50 [31,32]). Anal. Calcd. for $C_{10}H_8N_2Se_2$: Calcd. C, 38.23; H, 2.56; N, 8.92%. Found: C, 37.71; H, 2.45; N, 8.45%. IR (KBr, υ cm^{-1}): 3047, 1584, 1452, 778. ^{1}H NMR ($CDCl_3$) δ: 7.07 (1H, t, J = 5.6 Hz, C_5H_4), δ 7.53 (1H, t, J = 7.4 Hz, C_5H_4), δ 7.78 (1H, d, J = 7.8 Hz, C_5H_4), δ 8.44 (1H, d, J = 3.6 Hz, C_5H_4); ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 121.2 (C-5), 123.3 (C-3), 137.4 (C-4), 149.4 (C-6), 154.3 (Se–C); ^{77}Se{^{1}H} NMR ($CDCl_3$) δ: 447 ppm. MS (IT) m/z: 316 (M^+).

py_2Se (2a) IR (KBr, υ cm^{-1}): 3043, 1569, 1415, 755. ^{1}H NMR ($CDCl_3$) δ: 6.97–7.05 (1H, m, C_5H_4), δ 7.37–7.44 (2H, m, C_5H_4), δ 8.35–8.38 (1H, m, C_5H_4); ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 121.6 (C-5), 127.6 (C-3), 136.6 (C-4), 149.8 (C-6), 154.4 (Se–C); ^{77}Se{^{1}H} NMR ($CDCl_3$) δ: 518 ppm. MS (IT) m/z (%): 237 ([M + 1]$^+$, 100), 157 ([PySe-1]$^+$, 2).

2.2.2. Synthesis of pym_2Se_2 (**1b**) and pym_2Se (**2b**)

To a suspension of selenium powder (11.92 g, 151 mmol) in deoxygenated water, sodium borohydride (5.26 g, 138 mmol) was added at 0 °C under a nitrogen atmosphere and the reaction mixture was stirred for 2 h at room temperature to give a dark brown solution of Na_2Se_2. To this 2-bromopyrimidine (20 g, 125 mmol) was added and the reaction mixture was refluxed for 5 h till the solution turned dark orange. The hot reaction mixture was filtered and allowed to cool to room temperature whereupon an orange powder settled down which was separated by decantation and dissolved in hot methanol which on slow evaporation gave needle-shaped yellow crystals of dipyrimidyl diselenide (**1b**) (4.7 g, 24%). After separation of **1b**, the mother liquor on further concentration afforded cubic colorless crystals of dipyrimidyl monoselenide (**2b**) (5.4 g, 36%). Both the compounds were further purified by recrystallization.

pym_2Se_2 (1b) m.p. 156–158 °C. Anal. Calcd. for $C_8H_6N_4Se_2$: Calcd. C, 30.39; H, 1.91; N, 17.73%. Found: C, 30.91; H, 1.95; N, 17.15%. IR (KBr, υ cm^{-1}): 3037, 1555, 1367, 1155, 808. ^{1}H NMR ($CDCl_3$) δ: 7.05 (1H, t, J = 4.8 Hz, C_4H_3), δ 8.53 (2H, d, J = 4.8 Hz, C_4H_3); ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 118.4 (C-5), 157.9 (C-4, 6), 166.4 (C–Se); ^{77}Se{^{1}H} NMR ($CDCl_3$) δ: 490 ppm. MS (IT) m/z (%): 317 ([M – 1]$^+$, 17), 237 ([Pym_2Se, 100), 133 ([C_2N_2HSe]$^+$, 18).

pym_2Se (2b) m.p. 138–140 °C. Anal. Calcd. for $C_8H_6N_4Se$: Calcd. C, 40.52; H, 2.55; N, 23.63%. Found: C, 40.11; H, 2.45; N, 23.15%. IR (KBr, υ cm^{-1}): 3051, 1550, 1371, 1145, 808. ^{1}H NMR ($CDCl_3$) δ: 7.19 (1H, t, J = 4.8 Hz, C_4H_3), δ 8.66 (2H, d, J = 4.8 Hz, C_4H_3); ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 119.0 (C-5), 157.9 (C-4, 6), 168.0 (C–Se); ^{77}Se{^{1}H} NMR ($CDCl_3$) δ: 596 ppm. MS (IT) m/z: 237 [M – 1]$^+$, 133 [C_2N_2HSe]$^+$.

2.2.3. Synthesis of $(C_5H_4N)SeCH_2COOH$ (**3a**)

To a solution of dipyridyl diselenide (2.0 g, 6.53 mmol) in 60 ml of methanol, sodium borohydride (0.5 g, 13.07 mmol) was added under a flow of nitrogen at 0 °C and the reaction mixture was allowed to stir for 30 min forming a colorless solution of sodium selenolate. To this solution bromoacetic acid (1.82 g, 13.1 mmol) was added and the contents were stirred for 2 h at room temperature. The solvent was removed on rotavapour and the residue was dissolved in distilled water and extracted with ethyl acetate (3 × 100 ml). The organic phase was dried over sodium sulfate and the solvent was removed on rotavapor to yield a pale yellow solid which on recrystalization from ethyl acetate:hexane mixture (70:30) gave **3a** as a white crystalline solid (1.8 g, 64%). m.p. 121–123 °C; Anal. Calcd. for $C_7H_7NO_2Se$: C, 38.91; H, 3.27; N, 6.48%. Found: C, 38.61; H, 3.20; N, 6.15%. IR (KBr, υ cm^{-1}): 3073, 2927 (br, OH), 1693(s, C=O), 1585, 1454, 764. ^{1}H NMR(dmso-d_6) δ: 3.86 (2H, s, $^2J_{Se-H}$ = 6.00 Hz, $SeCH_2$), δ 7.16 (1H, t, J = 6.0 Hz, C_5H_4), δ 7.50 (1H, d, J = 7.8 Hz, C_5H_4), δ 7.63 (1H, t, J = 6.9 Hz, C_5H_4), δ 8.42 (1H, d, J = 4.5 Hz, C_5H_4); ^{13}C{^{1}H} NMR (dmso-d_6) δ: 25.4 ($^1J_{C-Se}$ = 67 Hz), 120.9 (C-5), 124.7 (C-3), 137.0 (C-4), 149.6 (C-6), 153.8 (C–Se), 171.5 (C=O); ^{77}Se{^{1}H} NMR (dmso-d_6) δ: 346 ppm. MS (IT) m/z (%): 216 ([M – 1]$^+$, 100), 197 ([PySeK]$^+$, 10), 158 ([PySe]$^+$, 16), 152 ([$C_3H_4SeO_2$]$^+$, 29).

The compounds **3b**–**3i** were prepared similar to **3a**, using corresponding diselenide and bromo functionalized compound (supplementary materials). The characterization data for **1a**, **3a**–**3c** were well in agreement with literature values [33].

2.3. X-ray crystallography

Single crystal X-ray data for 2,2′-dipyrimidyl diselenide (**1b**), 2,2′-dipyrimidyl selenide (**2b**) and 2-pyrimidyl seleno ethanoic acid (**3d**) were collected at room temperature (298 ± 2 K) on a Rigaku AFC 7S diffractometer using graphite monochromated Mo–Kα (λ = 0.71069 Å) radiation so that θ_{max} = 27.5°. The unit cell parameters (Table 1) were determined from 25 reflections measured by a random search routine. The intensity data were corrected for Lorenz, polarization and absorption effects with an empirical procedure [34]. The structures were solved by direct methods using SHELX-97 [35] and refined by full-matrix least squares methods. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were fixed in their calculated positions. The molecular structures were drawn by ORTEP [36].