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Synthesis, characterization, structures and antioxidant activity of nicotinoyl based organoselenium compounds

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ABSTRACT

A series of nicotinoyl based organoselenium compounds, [2-NC_5H_3(3-COOH)Se]$_2$ (**1**), [2-NC_5H_3(3-CO)Se–Se] (**2**), [2-NC_5H_3(3-$CONH_2$)Se]$_2$ (**3**), [2-NC_5H_3(3-CONHPh)Se]$_2$ (**4**), [2-NC_5H_3(3-CONHpyrimidine)Se]$_2$ (**5**), [2-NC_5H_3(3-CONHPh)SeBr] (**6**) and [2-NC_5H_3(3-CONHPh)SeI] (**7**) have been synthesized and characterized by absorption, IR, NMR (^{1}H, ^{13}C{^{1}H}, ^{77}Se{^{1}H}) and mass spectrometry. The crystal structures of [2-NC_5H_3(3-CO)Se–Se] (**2**) and [2-NC_5H_3(3-CONHPh)Se]$_2$ (**4**) have been determined. The structure of (**4**) revealed the existence of two intra-molecular Se···*X* (*X* = O and N) interactions, as a result of this, C–Se–Se–C torsion angle is unusually large (180°). The GPx mimicking activity of these compounds has been evaluated using methods based on ^{1}H NMR spectroscopy and HPLC. Free radical scavenging ability of the compounds was examined by DPPH and deoxyribose assay. All these studies indicated that the compound (**3**) not only showed highest GPx activity but also has a very good free radical scavenging ability thus making it a novel structure for development of nicotine based antioxidants.

1. Introduction

Selenium is an essential micronutrient for animals and humans and exists in the form of selenoenzymes. Glutathione peroxidase (GPx) is one of the major mammalian selenoenzymes [1,2]. GPx is an antioxidant enzyme that catalyzes the reduction of harmful hydroperoxides by using two molecules of glutathione (GSH) as a cofactor [3]. Having recognized the role of GPx enzymes in biochemical reactions, considerable efforts have been made to design and develop low-molecular weight organoselenium compounds, which can emulate the activity of naturally occurring selenoenzymes, GPx. Since the discovery of GPx like catalytic activity in a synthetic organoselenium compound, ebselen (**I**) [4,5], there is a growing interest in developing new classes of organoselenium compounds that exhibit GPx mimicking activity [3,6]. Accordingly, different groups have studied several families of GPx active organoselenium compounds. These compounds can readily be recognized by one of the following features, (i) compounds containing a covalent Se–N bond (e.g. **II**–**IV**) [7–9], (ii) compounds exhibiting weak intra-molecular Se···N or Se···O interactions (e.g. **V**–**VIII**) reported by Wilson [10], Tomoda [11], Mugesh [12,13], Singh [6,14], Wirth [15] and Jain [16] (iii) heterocyclic diselenides, e.g. 2-pyridyl diselenide (**IX**) [17] and (iv) compounds, both mono and diselenides, derived from alky groups bearing –OH, $-NH_2$, –COOH substituent at terminal positions (**X**–**XIII**) [18–21] (Scheme 1).

Nicotinic acid (vitamin B_3) and nicotinamide are important bio-molecules and are involved in a wide range of biological processes including energy production, synthesis of fatty acids, etc. They are precursors for the coenzymes NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate). They are important cofactors in numerous enzymatic redox reactions [22]. Nicotinamide has shown anti-inflammatory [23], chemo- and redox-sensing and antioxidant [24–27] activities.

With the above perspective, an intriguing idea could be to develop organoselenium compounds as antioxidants based on nicotinoyl group and the resulting compounds may show significant enhancement of GPx catalytic activity. Thus in pursuance of our interest on organoselenium compounds as antioxidant and radio-protectors we have designed and synthesized a series of

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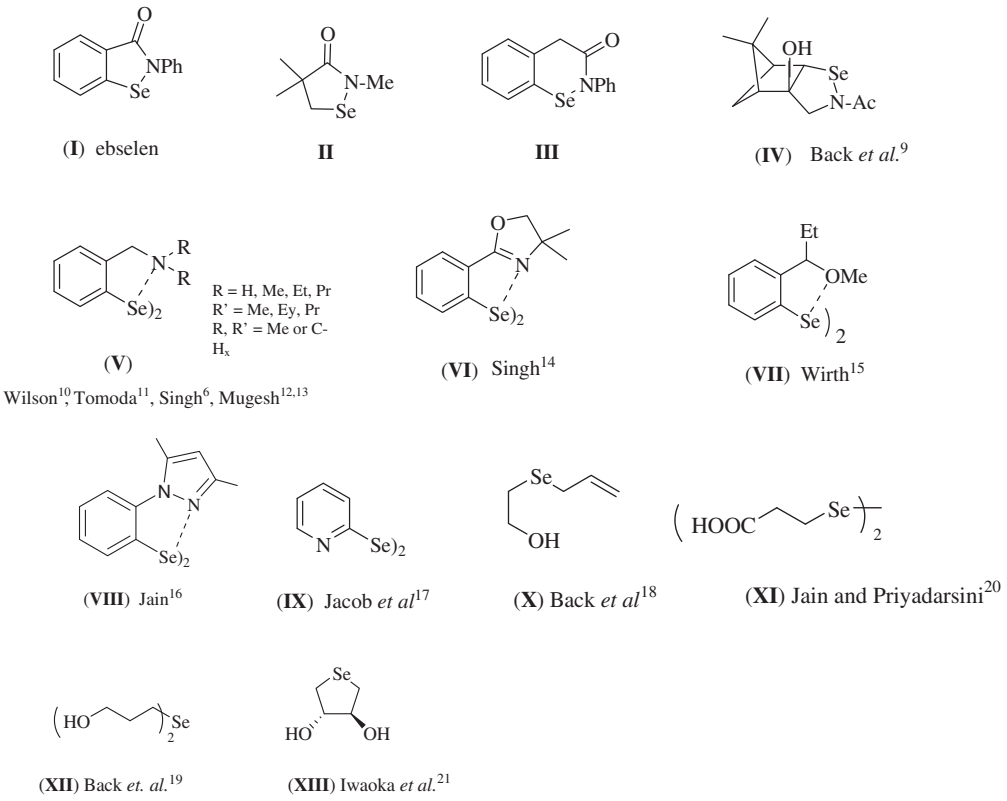


Scheme 1.

nicotinoyl based organoselenium compounds and evaluated their antioxidant properties. The results of this work are reported herein.

2. Experimental

2.1. Materials and methods

Elemental selenium (99.99%), sodium borohydride, 2-chloronicotinic acid, thionyl chloride, aniline, 2-amino−pyrimidine, hydrogen peroxide (30%), glutathione (GSH) and reduced dithiothreitol (DTT^{red}), 1,1-diphenyl 2-picryl hydrazyl (DPPH), thiobarbituric acid (TBA), 2-deoxyribose, trichloro acetic acid (TCA), ethylenediaminetetraacetic acid (EDTA), D-mannitol, butylated hydroxytoluene (BHT), L-ascorbic acid were obtained from commercial sources (Sigma/Aldrich). The compounds 2-chloro-3-nicotinoyl chloride [28], 2-chloro-3-nicotinamide, 2-chloro-3-(*N*-phenyl)nicotinamide, 2-chloro-3-(*N*-pyrimidine) nicotinamide were prepared by literature methods. Disodium diselenide (Na_2Se_2) was prepared by reduction of selenium metal with stoichiometric quantity of sodium borohydride in refluxing water or THF under a nitrogen atmosphere as a brown solution [29]. Freshly prepared solutions were used *in situ*. All syntheses were carried out under a nitrogen atmosphere in dry solvents. Solvents were purified and dried by standard procedures and were distilled prior to use. The purity of organoselenium compounds was tested initially by thin layer chromatography followed by column chromatography on silica gel (60/120 mesh size) using solvent mixtures as eluents.

Elemental analyses were carried out on a Thermo Fisher EA 1112 CHNS analyzer. Electronic spectra were recorded in methanol on a Jasco UV−vis spectrometer model V-630 PC. IR spectra were recorded on a JASCO FT IR-6100 spectrometer. NMR spectra were recorded on a Bruker Avance-II 300 MHz spectrometer operating at 300.13 (^{1}H), 75.47 ($^{13}C\{^1H\}$) and 57.25 MHz ($^{77}Se\{^1H\}$). ^{1}H and $^{13}C\{^1H\}$ NMR chemical shifts were relative to internal dmso peak ($\delta = 2.49$ ppm for ^{1}H and $\delta = 39.5$ for $^{13}C\{^1H\}$ NMR). The $^{77}Se\{^1H\}$ 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). A 90° pulse was used in every case. The mass spectra were recorded on a MS-500 Ion Trap (IT) Varian mass spectrometer at Sophisticated Analytical Instrumentation Facility (SAIF), Indian Institute of Technology-Bombay, Mumbai.

2.2. Synthesis of organoselenium compounds

2.2.1. Synthesis of [2-NC_5H_3(3-COOH)Se]$_2$ (**1**)

To a THF solution of Na_2Se_2 (prepared from selenium metal (3.50 g, 44.32 mmol) and sodium borohydride (1.75 g, 46.26 mmol) in refluxing THF (100 ml) under nitrogen), solid 2-chloronicotinic acid (6.96 g, 44.17 mmol) was added with stirring and the contents were refluxed for 3 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue was treated with water (50 ml). The aqueous phase was extracted with chloroform−methanol (80:20). Combined organic phases were washed with sodium bicarbonate (5% aq.) followed by water, dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated in vacuum and the residue was column chromatographed using chloroform−methanol mixture (70:30 v/v). The solvents from the eluted solution were evaporated in vacuum to yield a greenish yellow solid (2.78 g, 31%), m.p. 218−220 °C (decomp). Anal. for $C_{12}H_8N_2O_4Se_2$; Calcd: C, 35.84; H, 2.00; N, 6.97%. Found C, 35.64; H, 2.18; N, 6.92%. UV−vis (in MeOH) (λ_{max} in nm): 220, 275, 393. IR in KBr (υ cm^{-1}): 3375 (OH), 1645

(CO). ^{1}H NMR (dmso-d_6) δ: 7.07 (dd, 7.5, 4.5 Hz, H-5, py); 8.06 (dd, 1.8, 7.5 Hz, H-4 py); 8.29 (dd, 1.5, 4.8 Hz, H-6, py). ^{13}C{^{1}H} NMR (dmso-d_6) δ; 119.0, 133.4 (C–Se), 136.9, 149.5, 162.1 (C–COOH); 169.0 (CO). ^{77}Se{^{1}H} NMR (dmso-d_6) δ: 506 ppm. Mass (m/z): 402 (M^+), 236 ($Se_2C_5H_4N$).

*2.2.2. Synthesis of [2-NC_5H_3(3-CO)Se–Se] (**2**)*

To a brown THF solution of Na_2Se_2 (prepared from selenium metal (2.42 g, 30.65 mmol) and sodium borohydride (1.16 g, 30.66 mmol) in refluxing THF (80 ml)) solid 2-chloro-3-nicotinoyl chloride (2.70 g, 15.34 mmol) was added and the contents were refluxed for 3 h under a nitrogen atmosphere with stirring. The residue was treated with water (50 ml). After aqueous work-up and extraction with chloroform, the crude product was column chromatographed using ethyl acetate-petroleum ether mixture (10:90 v/v). After the solvents evaporation, saffron coloured crystals of the title compound were obtained (863 mg, 21%), m.p. 120–122 °C. Anal. for $C_6H_3N_1O_1Se_2$; Calcd : C, 27.40; H, 1.15; N, 5.32%. Found; C, 27.66; H, 1.19; N, 5.31%. UV–vis (in MeOH) (λ_{max} in nm): 282, 375. IR in KBr (υ cm^{-1}): 1767 (CO). ^{1}H NMR (dmso-d_6) δ: 7.28 (d,d, 8, 6 Hz, CH-5, py); 8.11 (d, 6 Hz, CH-4 py); 8.77 (br, C-6, py); ^{13}C{^{1}H} NMR (dmso-d_6) δ: 120.7, 128.4 (C–Se), 136.9, 155.1, 167.5 (C–CO); 195.4 (CO). ^{77}Se{^{1}H} NMR (dmso-d_6) δ: 439 ppm (Se–C_5H_3N), 628 (Se–CO). Mass (m/z): 263 (M^+).

*2.2.3. Synthesis of [2-NC_5H_3(3-$CONH_2$)Se]$_2$ (**3**)*

To an aqueous solution of Na_2Se_2 (prepared from selenium metal (1.00 g, 12.66 mmol) and $NaBH_4$ (434 mg, 11.47 mmol) in 60 ml distilled water) was added a solution of 2-chloro-3-nicotinamide (2.00 g, 12.77 mmol) with stirring under a nitrogen atmosphere. The reaction mixture was refluxed for 2 h with stirring. After cooling to room temperature, product was extracted with a chloroform–methanol (3:1 ratio) mixture. The organic phase was separated, washed with sodium bicarbonate solution followed by water, dried over anhydrous sodium sulphate, and filtered. The filtrate was concentrated under vacuum and the residue was column chromatographed with chloroform–methanol (90:10) mixture. The solution on evaporation afforded yellow powder (yield 216 mg, 8%; due to degradation during column purification product yield was significantly reduced), m.p. 126–128 °C. Anal. for $C_{12}H_{10}N_4O_2Se_2$; Calcd: C, 36.02; H, 2.52; N, 14.00%. Found C, 34.64; H, 2.73; N, 13.47%. UV–vis (in MeOH) (λ_{max} in nm): 326, 402. IR in KBr (υ cm^{-1}): 3250 (NH_2), 1671 (CO). ^{1}H NMR (dmso-d_6) δ: 7.28 (d, d, 6 Hz, CH-5, py); 8.35, 7.84 (NH_2); 8.16 (d, 7.5 Hz, py); 8.49 (d, 5 Hz, py); ^{13}C{^{1}H} NMR (dmso-d_6) δ: 119.7, 128.1 (C–Se),135.5, 151.5, 160.5 (C-3, py); 168.2 (CO). ^{77}Se{^{1}H} NMR (dmso-d_6) δ: 525 ppm. Mass (m/z): 400 (M^+).

*2.2.4. Synthesis of [2-NC_5H_3(3-CONHPh)Se]$_2$ (**4**)*

To an aqueous solution of Na_2Se_2 (prepared from selenium metal (1.46 g, 18.46 mmol) and $NaBH_4$ (704 mg, 18.61 mmol) in 150 ml water), 2-chloro-3-(*N*-phenyl)nicotinamide (4.30 g, 18.48 mmol) was added in small instalments with stirring under a nitrogen atmosphere. The reactants were refluxed with stirring for 3 h, whereupon yellow crystals of the title compound were formed. The crystals were filtered through a sintered funnel and washed thoroughly with distilled water followed by ethyl acetate–hexane (1:1) mixture and dried *in vacuo* (2.78 g, 55%), m.p. 217–219 °C. Anal. for $C_{24}H_{18}N_4O_2Se_2$; Calcd: C, 52.19; H, 3.28; N, 10.14% Found C, 52.02; H, 3.49; N, 10.30%. UV–vis (in MeOH) (λ_{max} in nm): 230, 313, 407. IR in KBr (υ cm^{-1}): 3177 (NH), 1651 (CO). ^{1}H NMR (dmso-d_6) δ: 7.11 (t, 8 Hz, H-4, Ph); 7.24 (t, 7 Hz, H-5, py); 7.36 (t, 8 Hz, H-3, 5, Ph); 7.69 (d, 8 Hz, H-2, 6, Ph); 8.01 (d, 6 Hz, 1H, py); 8.32 (d, 6 Hz, 1H, py); 12.14 (s, NH). ^{13}C{^{1}H} NMR (dmso-d_6) δ: 116.5, 124.4, 138.9, 140.7 (Ph); 119.9, 129.3, 138.6 (C–Se), 142.4, 163.0 (py); 167.9 (CO). ^{77}Se{^{1}H} NMR (dmso-d_6) δ: 352 ppm. Mass (m/z) 552 (M^+): 276 (1/2 M^+ or NC_5H_3(CONHPh)Se).

*2.2.5. Synthesis of [2-NC_5H_3(3-CONHpyrimidine)Se]$_2$ (**5**)*

To a THF solution of Na_2Se_2 (prepared from selenium metal (1.45 g, 18.36 mmol) and sodium borohydride (700 mg, 18.50 mmol) in 50 ml refluxing THF), 2-chloro-3-(*N*-pyrimidine) nicotinamide (4.30 g, 18.32 mmol) in THF was added with stirring under a nitrogen atmosphere. The reaction mixture was refluxed for 2 h. The solvent was evaporated under vacuum. The residue was treated with water (40 ml) and the product was extracted with chloroform. Organic phase was washed with sodium bicarbonate (5% aqueous) followed by water, dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under vacuum and the residue was chromatographed using ethyl acetate–hexane (30:70) mixture. The eluted solution on vacuum drying afforded a brown solid (yield 2.64 gm 52%), m.p. 222–224 °C (decomp). Anal. for $C_{20}H_{14}N_8O_2Se_2$; Calcd: C, 43.18; H, 2.54; N, 20.14% Found C, 43.00; H, 2.18; N, 20.20%. UV–vis (in MeOH) (λ_{max} in nm): 250, 298, 356, 370. IR in KBr (υ cm^{-1}): 3112 (NH), 1670 (CO). ^{1}H NMR (dmso-d_6) δ: 7.23 (t, H-5 py) + H-4 (pyrimidine); 8.04 (d, 6 Hz, py); 8.30 (d, 7 Hz, py); 8.68 (d, 5 Hz, H-3, 5; pyrimidine); 12.62 (br, NH). ^{13}C{^{1}H} NMR (dmso-d_6) δ: 123.6, 128.5 (C–Se), 140.5, 157.5 (py ring), 166.1 (CO), 110.3, 148.2, 152.1, 156.1 (pyrimidine carbons). ^{77}Se{^{1}H} NMR (dmso-d_6) δ: 355 ppm. Mass (m/z), 557 (M^+), 278 (1/2 M^+).

*2.2.6. Synthesis of [2-NC_5H_3(3-CONHPh)SeBr] (**6**)*

To a stirred dichoromethane solution (35 ml) of [2-NC_5H_3(3-CONHPh)Se]$_2$ (2.50 g, 4.52 mmol), a carbon tetrachloride solution of bromine was added drop wise till the light brown colour of bromine persisted. The reactants were stirred for 3 h at room temperature whereupon a yellow precipitate formed which was filtered through a sintered funnel and washed thoroughly with carbon tetrachloride and dried under vacuum (yield 3.06 g, 95%), m.p. 205–207 °C. Anal. for $C_{12}H_9BrN_2O_1Se$; Calcd: C, 40.48; H, 2.55; N, 7.85%. Found; C, 41.30; H, 2.92; N, 7.77%. UV–vis (in MeOH) (λ_{max} in nm): 268, 333. IR in KBr (υ cm^{-1}): 3250 (NH), 1626 (CO). ^{1}H NMR (dmso-d_6) δ: 7.27 (t, Ph + py); 7.44 (t); 7.56 (d); 7.94 (t); 8.47 (d, py); 8.99 (d, py); 11.24 (s, NH). ^{13}C{^{1}H} NMR (dmso-d_6) δ: 120.0, 123.6, 124.6, 129.3, 133.6 (C–Se), 138.6, 139.1, 150.9 (C-3), 164.0 (CO). ^{77}Se {^{1}H} NMR (dmso-d_6) δ: 768 ppm. Mass (m/z): 356 (M^+); 276 (M – Br); 197 ($NC_5H_3CONHPh$).

*2.2.7. Synthesis of [2-NC_5H_3(3-CONHPh)SeI] (**7**)*

To a stirred dichloromethane solution (35 ml) of [2-NC_5H_3(3-CONHPh)Se]$_2$ (2.00 g, 3.62 mmol), a carbon tetrachloride solution of iodine was added drop wise till the purple colour of iodine persisted. The reactants were stirred for 3 h at room temperature whereupon a brown solid was precipitated which was filtered through a sintered funnel, washed with carbon tetrachloride and dried under vacuum (yield 2.84 g, 97%), m.p. 201–203 °C. Anal. for $C_{12}H_9IN_2OSe$; Calcd : C, 35.76; H, 2.25; N, 6.95%. Found: C, 35.76; H, 2.25; N, 6.86%. UV–vis (in MeOH) (λ_{max} in nm): 240, 282. IR in KBr (υ cm^{-1}): 3214 (NH), 1637 (CO). ^{1}H NMR (dmso-d_6) δ: 7.16 (t, 7.2 Hz, CH-4, Ph); 7.35–7.42 (m, Ph + py); 7.32 (d, 7.8 Hz, CH-2,6, Ph); 8.29 (d.d, 7, 1.5 Hz, CH-4, py); 8.52 (d, d, 6, 1.5 Hz, CH-6, py); 10.60 (s, NH). ^{13}C{^{1}H} NMR (dmso-d_6) δ: 120.1, 122.2, 124.5, 126.2, 128.9, 129.4, 136.0, 136.7, 151.7(CO), 153.4. ^{77}Se{^{1}H} NMR (dmso-d_6) δ: 524 ppm; Mass (m/z): 403 (M^+); 246, 237.

2.3. GPx like catalytic activity

The GPx like catalytic activity of these compounds has been evaluated by HPLC and ^{1}H NMR spectroscopy. In HPLC assay GPx

like activity was monitored by following the ratio of the depletion in the concentration of glutathione reduced (GSH) and increase in the concentration of oxidized glutathione (GSSG). In our model system [30], reaction was initiated by adding H_2O_2 (320 μM) to a mixture of GSH (160 μM) and organoselenium compounds (10 μM) as catalysts and leaving it for 5 min. The GSH and GSSG were separated by HPLC on a reverse phase C18 column using a mobile phase of aqueous solution containing 2% methanol in 0.1% trifluoroacetic acid (TFA) and detected at 210 nm. The reaction mixture 40 μL was injected into the column and the reaction was monitored till 310 min, and the recorded values are an average of 2 injections. By plotting the concentration of GSSG vs. time in mins t_{50}, the time needed to perform 50% of the reaction was determined.

The catalytic activity of organoselenium compounds as GPx mimics was also evaluated by NMR route employing the method reported by Iwaoka *et al.* [21,31]. In this method reduction of hydrogen peroxide, using DTT^{red} (reduced dithiothreitol) as thiol cofactor was monitored by ^1H NMR spectroscopy. In a typical experiment DTT^{red} (23.1 mg, 0.15 mmol) and organoselenium compound (0.015 mmol) as a catalyst were dissolved in CD_3OD (0.5 ml) and the reaction was initiated by addition of freshly standardized H_2O_2 (47.6%) (9.15 μl, 0.15 mmol). At this point reaction was considered to be at zero time. The progress of the reaction was monitored by ^1H NMR spectroscopy. The relative concentration of thiol (DTT^{red}, δ 3.67 ppm for CH protons) and disulfide (DTT^{ox}, δ 3.49 ppm for CH protons) was estimated by integrating the respective resonances. The time required for 50% oxidation of DTT^{red} to DTT^{ox} was calculated which in turn was a measure of 50% reduction of H_2O_2 by the cofactor thiol (DTT^{red}). For control, similar experiment was performed in the absence of an organoselenium compound.

2.4. Free radical scavenging ability

2.4.1. DPPH radical assay

Radical scavenging ($H^{\bullet}$) activity of organoselenium compounds against 1,1-diphenyl 2-picryl hydrazyl (DPPH) radical was measured spectrophotometrically [32]. Accordingly working solution was prepared in 3 ml HPLC grade methanol with the concentration ranging from 5, 10, 25, 50 μM of test compounds and positive control butylated hydroxytoluene (BHT) and that of DPPH was 100 μM 1 ml of test compounds of various concentrations were mixed to 2 mL of DPPH in methanol. The absorbance at 517 nm was measured after incubating the reaction mixture for 30 min at room temperature. Inhibition (I) of DPPH radical was calculated using the equation $I\,(\%) = 100 \times (A_o - A_s)/A_o$, where A_o is the absorbance of control (having all the regents except test compounds), and A_s is the absorbance of the tested compound. Results were compared by using BHT as positive control.

2.4.2. 2-Deoxyribose assay

$OH^{\bullet}$ radical scavenging capacity was studied in non-site specific deoxyribose assay [33]. Solutions of EDTA (5 mM), 100 μL, $FeCl_3$ (1 mM), 100 μL, 2-deoxyribose, 100 μL, H_2O_2 (10 mM), 100 μL, test compounds, 200 μL (concentrations ranging from 5 to 50 μM), phosphate buffer (50 mM, pH 7.4), 300 μL and ascorbic acid (15 mM), 100 μL were mixed sequencially and the resulting mixture was incubated at 37 °C for 1 h. To this incubated mixture added 250 μL 4% (W/V) solution of thiobarbituric acid (TBA) in 0.05 M NaOH and 250 μL of 11.2% (W/V) solution of trichloro acetic acid (TCA). The reaction mixture was heated on water bath at approximately 100 °C for 30 min to develop pink colour and then cooled in ice. The absorbance was measured at 532 nm. Inhibition of 2-deoxyribose from degradation was calculated the same way as described in DPPH radical assay. Mannitol was used as positive control.

2.5. X-ray crystallography

Single crystal X-ray diffraction data for [2-NC_5H_3(3-CO)Se–Se] (**2**), and [2-NC_5H_3(3-CONHPh)Se]$_2$ (**4**) were collected at room temperature (298 ± 2 K) on a Rigaku AFC 7S diffractometer using graphite monochromated Mo-Kα ($\lambda = 0.71069$ Å) radiation so that $\theta_{max} = 27.5°$. 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].

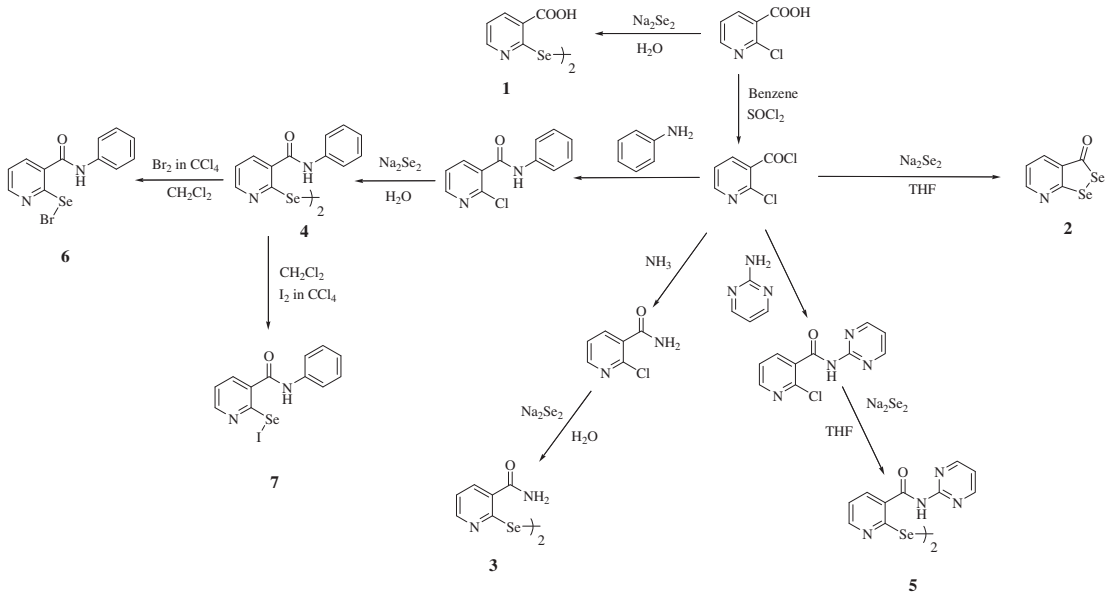
3. Results and discussion

3.1. Synthesis and spectroscopy

Treatment of 2-chloronicotinic acid with Na_2Se_2 in THF yields a greenish yellow diselenide (**1**). Various other selenides were prepared using 2-chloro-3-nicotinoyl chloride (Scheme 2). Thus, the reaction of the latter with Na_2Se_2 in THF afforded a saffron coloured cyclic diselenide (**2**). The reactions of 2-chloro-3-nicotinoyl chloride with various amines yield the corresponding amides which when treated with Na_2Se_2 gave dislenides **3**–**5**. Oxidation of **4** with halogens in CCl_4 gave halo compounds, 2-NC_5H_3(3-CONHPh)Se*X* (*X* = Br (**6**) and I (**7**)). The reactions of diselenides with iodine have been known to yield either selenenyl iodide (RSeI) [14,37] or iodine adduct of diselenide ($R_2Se_2.I_2$)

Table 1
Crystallographic and structural refinement data for [2-NC_5H_3(3-CO)Se–Se] (**2**) and [2-NC_5H_3(3-CONHPh)Se]$_2$.dmso (**4**.dmso).

Compound	[2-NC_5H_3(3-CO)Se–Se] (**2**)	[2-NC_5H_3(3-CONHPh)Se]$_2$ (**4**)
Chemical formula	$C_6H_3NOSe_2$	$C_{24}H_{18}N_4O_2Se_2$.dmso
Formula weight	263.01	624.42/check 630
Colour of crystal	Orange	Yellow
Crystal size (mm)	0.30 × 0.15 × 0.05	0.30 × 0.20 × 0.05
Crystal system	Monoclinic/$P2_{1/c}$	Monoclinic/$C_{2/c}$
a (Å)	5.2746 (16)	21.690 (7)
b (Å)	8.366 (4)	8.761 (4)
c (Å)	16.000 (6)	13.834 (8)
β (°)	95.46 (3)	102.30 (3)
V (Å^3)	702.8 (5)	2568.4 (19)
Z	4	4
D_c (g/cm^3)	2.486	1.615
μ(Mo-*K*α) mm^{-1}/*F* (000)	10.439/488	2.996/1240
Limiting indices	$-6 \le h \le 6$; $-6 \le k \le 10$; $-11 \le l \le 20$	$-15 \le h \le 28$; $0 \le k \le 11$; $-17 \le l \le 17$
θ range for data collection	2.56–27.43	2.52–27.51
No. of reflections collected	1577	2947
No. of independent reflections	805	1964
Data/Restraints/Parameters	1577/0/91	2947/0/173
R indices [$I > 2\sigma(I)$]	$R1 = 0.0437$, $wR2 = 0.0847$	$R1 = 0.0520$, $wR2 = 0.1320$
R indices (all data):	$R1 = 0.1478$, $wR2 = 0.1150$	$R1 = 0.0961$, $wR2 = 0.1609$
$(\Delta/\sigma)_{max}$	0.000	0.000
$(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$	0.792*e* Å^{-3}, −0.964*e* Å^{-3}	1.116*e* Å^{-3}, −1.052*e* Å^{-3}
Goodness-of-fit on F^2	0.970	1.051



Scheme 2.

[38,39] depending on the nature of organic groups attached to selenium. The selenenyl iodides have been isolated when *R* is either a bulky group [37] or a group, which facilitates intra-molecular secondary Se···N interactions [14].

The electronic spectra of these compounds in methanol displayed absorptions in the region 230–407 nm. 2-Chloronicotinic acid exhibited absorption at λ_{max} 220, 268 nm. The longest wavelength maximum at ~400 nm in **3** and **4**, which was not observed in the spectra of other compounds, could be due to $n \rightarrow \sigma^*$ transition as similar absorption has been attributed in diorganoditellurides [40,41]. The IR spectra of these compounds showed a carbonyl absorption in the region 1767–1626 cm^{-1}.

The ^1H NMR spectra showed expected resonances and peak multiplicities. The CH-6 proton resonance of pyridyl group appeared in a wide range of δ 8.17–8.99 ppm. The CH-6 proton resonance of **4** (δ 8.32 ppm) is considerably deshielded on oxidation to the corresponding halo compounds (δ 8.99 ppm in **6** and 8.52 ppm in **7**). In contrast the NH proton resonance of **4** (δ 12.14 ppm) is shielded in the halo derivatives (δ 11.24 ppm in **6** and 10.60 ppm in **7**). The C–Se resonance in the ^{13}C NMR spectra of diselenides appeared at ~129 ppm, which is deshielded for the bromo compound (**6**) (133.6 ppm). The carbonyl carbon resonances, except **2**, appeared in the range 164.0–169.0 ppm. In the case of **2** this resonance is considerably deshielded (δ 195.4 ppm). The Se_2 moiety in **2** has two distinct selenium atoms, one bonded to pyridyl ring while the other is bound to the carbonyl carbon atom. Accordingly the ^{77}Se NMR spectrum of **2** exihibited two signals at δ 439 and 628 ppm, the former attributed to the selenium bound to the pyridyl ring. The two selenium atoms in the Se_2 moiety of **1**, **3**–**5** are chemically equivalent, accordingly their ^{77}Se NMR spectra showed single resonances. The ^{77}Se NMR resonances for selenenyl halides are considerably deshielded (δ 768 ppm for **6** and δ 524 ppm for **7**) with reference to the corresponding diselenide **4** (δ 352 ppm). The observed shifts are within the range reported for RSeX compounds in literature [14,42].

3.2. Crystal structures of **2** and **4**

Molecular structures of [2-NC_5H_3(3-CO)Se–Se] (**2**) and [2-NC_5H_3(3-CONHPh)Se]$_2$ (**4**) determined by single crystal X-ray diffraction analysis are shown in Figs. 1 and 2 and the selected inter atomic parameters are given in Tables 2 and 3. The structure of **2** is an example of a limited number of cyclic diselenides which are structurally characterized. The Se–Se distance in **2** (2.3378(13) Å) is similar to those reported in cyclic diselenides, e.g., 6-methoxy-3-*H*-[1,2]diselenolo[3,4-*b*]quinoline (2.354 Å) [43], 4,4-diphenyl-2,3-diselenabicyclo[3.3.0]oct-7-ene (2.322(2) Å) [44], trans-1,2-diselenane-4,5-diol (2.3108(9) Å) [45], and 1,8:4,5-bis(diseleno)naphthalene (2.364(1) Å) [46]. The C–Se distances are similar to trans-1,2-diselenane-4,5-diol [45] and 1,8:4,5-bis(diseleno) naphthalene [46] but are shorter than those reported for 4,4-diphenyl-2,3-diselenabicyclo[3.3.0]oct-7-ene (2.121(2) and 2.201(13) Å) [44]. The C–Se–Se–C torsion angle (3.51°) can be compared with 1,8:4,5-bis(diseleno)naphthalene (4.4°) [46], but is significantly different from an acyclic diselenide, trans-1,2-diselenane-4,5-diol (53.93(19)°) [45], which adopts a distorted chair conformation.

The Se–Se distance in **4** (2.3916(12) Å) is slightly longer than those reported in various pyridyl diselenides such as 2,2-dipyridyldiselenide (2.2969(9) Å) [47], 4,4-dimethyl-2,2-dipyridyldiselenide (2.2973(7) Å) [48], 6,6-dimethyl-2,2-

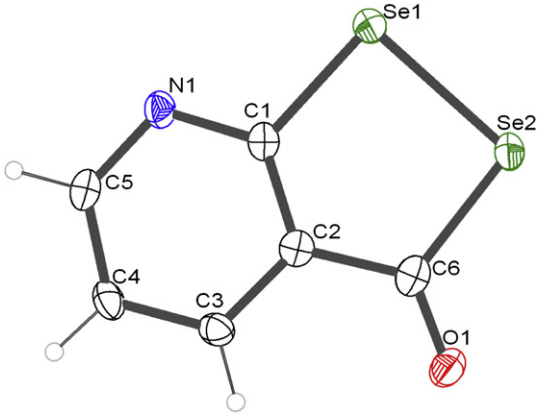


Fig. 1. Molecular structure of [2-NC_5H_3(3-CO)Se–Se] (**2**) with 50% thermal ellipsoid probability.

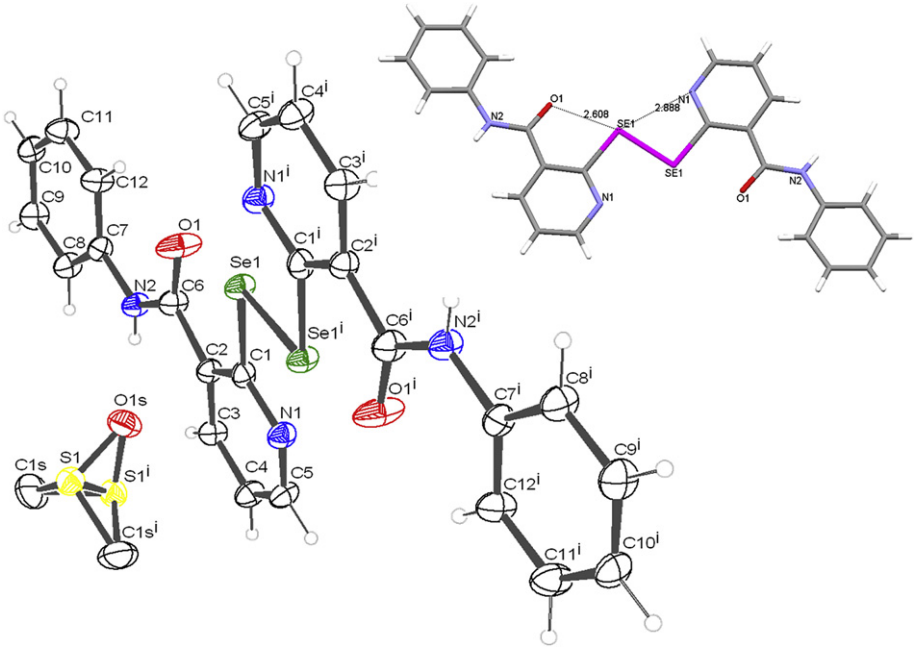


Fig. 2. ORTEP drawing with crystallographic numbering scheme of $[2\text{-}NC_5H_3(3\text{-}CONHPh)Se]_2$.dmso (**4**.dmso) with 50% thermal ellipsoid probability. Inset shows weak Se···N and Se···O interatctions.

dipyridyldiselenide (2.2935(1) Å) [49] and bis(3,5-dimethyl-2-dipyridyl)diselenide (2.352(2) Å) [50], and also in other derivatives, e.g. $[Me_2NC_4H_2N_2Se_2]$ (2.3162(16) Å) [51] and $(2\text{-}Pr^n{}_2NCH_2C_6H_4Se)_2$ (2.346 Å) [13]. The pyridyl nitrogen atoms are in cis, cis position relative to Se(1)–Se(1)′ group. The C–Se distances (1.93 Å) are well in agreement with the values reported for organoselenium compounds. An interesting feature of the structure is intra-molecular Se···*X* interactions. The molecule shows intra-molecular secondary Se1′···N1 (2.887 Å) and Se1···O1 (2.608 Å) interactions. The Se···N and Se···O distances are significantly shorter than the sum of van der Waals radii of Se–N and Se–O [6]. Each selenium atom in **4** is weakly coordinated to the oxygen atom of the carbonyl group of the same pyridyl ring with which it is bonded and also to the nitrogen atom of the other pyridyl ring. The two intra-molecular Se···N and Se···O interactions appear to be responsible for the observed large C–Se–Se–C torsion angle of 180°. The C–Se–Se–C torsion angle in several pyridyl disenides is ~90° [40,41,52] while it is 180° in bis(3,5-dimethyl-2-pyridyl)diselenide [50]. The latter molecule exhibits weak Se···N interactions. Compound **4** represents the first example where two intra-molecular Se···*X* (*X* = N or O) secondary interactions exist in a diselenide.

3.3. GPx mimicking activity

To assess the GPx mimicking activity of organoselenium compounds a number of methods have been employed. These include absorption spectroscopy based NADPH-reductase coupled assay, HPLC based thiol-disulfide conversion assay [12] and ^{1}H NMR based methods [21]. In the present study, the latter two methods have been used for evaluation of GPx mimicking activity of **1**-**7** [21,31]. In the ^{1}H NMR assay, H_2O_2 induced oxidation of DTT^{red} to DTT^{ox} is followed. As the reaction progresses the resonances at $\delta = 2.63$, 3.67 ppm for DTT^{red} decreases with concomitant increase of signals at $\delta = 2.87$, 3.03, 3.49 ppm due to DTT^{ox}. The catalytic efficiency of nicotinoyl based organoselenium compounds was determined by time the required for 50% conversion of DTT^{red} to DTT^{ox}, which is termed as t_{50}. The oxidation of DTT^{red} was 50% completed within 9 min ($t_{50} = 9$ min) when $[2\text{-}NC_5H_3(3\text{-}COOH)Se]_2$ (**1**) (0.015 mmol, 10 mol %) was used as a catalyst. The compound $[2\text{-}NC_5H_3(3\text{-}CONH_2)Se]_2$ (**3**) exhibited the best activity among all the derivatives. At the concentration of 0.015 mmol (10 mol %) the reaction at the start of the reaction could not be followed as complete conversion of DTT^{red} to DTT^{ox} was observed instantaneously. Therefore it was used at a lower concentration (0.003 mmol; 2 mol %), where the t_{50} was ~4 min. A comparison of GPx mimicking activities of the nicotinoyl based organoselenium compounds (**1**–**7**) is shown in Fig. 3 while the t_{50} values are given in Table 4. From these results, GPx mimicking activities are in the order **3** > **7** > **4** > **6** > **1** > **5** > **2**.

The GPx mimicking activity of these compounds has also been evaluated by HPLC method. Several groups have employed

Table 2
Selected bond lengths (Å) and angles (°) for $[2\text{-}NC_5H_3(3\text{-}CO)Se\text{–}Se]$ (**2**).

Se1–Se2	2.3378 (13)	C1–N1	1.350 (9)
C1–Se1	1.944 (8)	C5–N1	1.366 (10)
C6–Se2	1.959(9)	C1–C2	1.393 (11)
C6–O1	1.223 (9)	C2–C6	1.484 (10)
N1–C1–Se1	115.6 (6)	Se2–C6–O1	121.3 (6)
C1–Se1–Se2	90.9 (2)	Se2–C6–C2	114.6 (6)
Se1–Se2–C6	93.7 (3)	C2–C1–Se1	119.9 (6)

Table 3
Selected bond lengths (Å), bond angles (°) and torsion angles (°) for $[2\text{-}NC_5H_3(3\text{-}CONHPh)Se]_2$ (**4**).

Se1–C1	1.923 (6)	N1–C1	1.324 (6)
Se1–Se2	2.3916 (12)	N1–C5	1.350 (7)
C6–O1	1.226 (7)	Se1···O1	2.608
N2–C7	1.349 (6)	Se1′···N1	2.887
N2–C7	1.420 (6)		
C1–Se1–Se1′	92.83 (14)	N2–C6–O1	121.9 (5)
C2–C1–Se1	121.0 (4)	C2–C6–O1	119.3 (4)
N1–C1–Se1	115.8 (4)	C2–C6–O1	118.8 (5)
C1′–Se1′–Se1–C	180	C2–C1–Se1–Se1′	173.1 (4)
N1–C1–Se1–Se1′	−7.3 (4)		

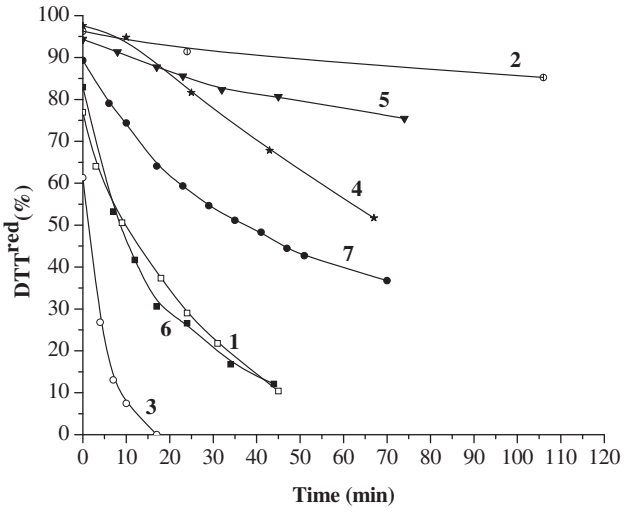


Fig. 3. Percentages of residual DTT^{red} as a function of the reaction time in the oxidation of DTT^{red} with H_2O_2 in the presence of organoselenium catalysts in CD_3OD. Reaction conditions: $[DTT^{red}]_0 = [H_2O_2]_0 = 0.15$ mmol and [selenide] = 0.015 mmol.

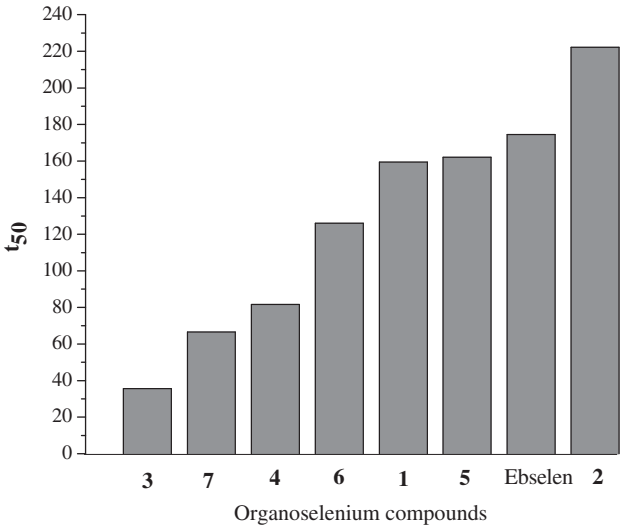


Fig. 4. t_{50} Bar graph showed by catalysts by HPLC method.

oxidation of thiol to disulfide by hydrogen peroxide [9,53,54]. In the present study oxidation of GSH (reduced glutathione) to GSSG (oxidized glutathione) by hydrogen peroxide was monitored by HPLC using a UV detector. Chromatograms due to absorptions of both GSH and GSSG were monitored every hour upto 3 h. Presence of selenium compound increased the rate of conversion of GSH to GSSG. The t_{50} value i.e., the time required for 50% conversion of GSH to GSSG was determined for each derivative (Table 4). As observed in NMR assay, the profile for the GPx like activity followed the trend **3** > **7** > **4** > **6** > **1** > **5** > **2** > ebselen (Fig. 4). It is evident that the compound **3** is the most potent catalyst and also exhibits better activity than the well-known compound ebselen.

The t_{50} values measured by ^1H NMR spectroscopy and HPLC method are different (Table 4), although the trend of GPx mimicking activity for these compounds evaluated by different methods is the same. The reasons for such discrepancy are mainly due to usage of different thiols. In NMR method, a dithiol (DTT^{red}) which being a stronger reducing agent, leads to facile reduction of diselenide linkage [3,55] while in the HPLC method GSH, a monothiol, is used and reduction of diselenide bond by a monothiol, would be very slow [3,56].

Table 4
Evaluation of GPx like catalytic activity of organoselenium compounds by HPLC and ^1H NMR spectroscopy.

Compounds	t_{50} by HPLC (min) at 10 μM catalyst	t_{50} by NMR (min)
$[2\text{-}NC_5H_3(3\text{-}COOH)Se]_2$ (**1**)	159.45	17[a]
$[2\text{-}NC_5H_3(3\text{-}CO)Se{-}Se]$ (**2**)	174.53	>120[a]
$[2\text{-}NC_5H_3(3\text{-}CONH_2)Se]_2$ (**3**)	35.65	4[c]
$[2\text{-}NC_5H_3(3\text{-}CONHPh)Se]_2$ (**4**)	81.64	73[b]
$[2\text{-}NC_5H_3(3\text{-}CONHpyrimidine)Se]_2$ (**5**)	162.04	>120[a]
$[2\text{-}NC_5H_3(3\text{-}CONHPh)SeBr]$ (**6**)	126.04	12[a]
$[2\text{-}NC_5H_3(3\text{-}CONHPh)SeI]$ (**7**)	66.56	47[c]
Ebselen	220.5	–
Selenocystein	147	–

Concentration of the catalyst used for NMR method.
[a] 10 mol%.
[b] 2.5 mol%.
[c] 2 mol%.

3.4. Free radical scavenging assays

3.4.1. DPPH assay

The hydrogen atom or electron donating abilities of the synthesized nicotinamide derivatives were measured by following the change in the absorbance due to DPPH at 517 nm as a function of the concentration of the selenium compound as shown in Fig. 5. The IC50 values, i.e. the concentration of selenium compound required to scavenge 50% of DPPH free radical were estimated and listed in Table 5. The results indicated that the free radical scavenging ability was highest for **3** followed by **4** and BHT. Compounds **5**–**7** did not show 50% of inhibition even at the highest soluble concentration. The order of radical scavenging ability of their highest concentration (50 μM) is **3** > **4** > BHT > **5** > **6** (Fig. 6, Table 5). It was found that compounds **1** and **2** did not exhibit any significant scavenging activity even at equimolar concentration ratios of the selenium compound and DPPH.

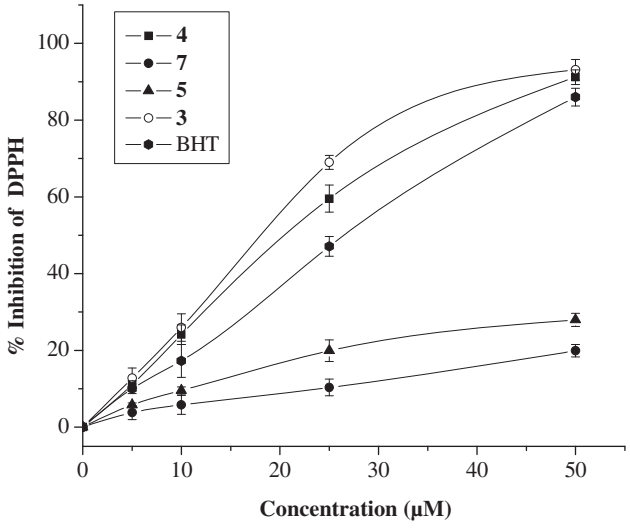


Fig. 5. Scavenging activity (%) on DPPH radicals by nicotinic acid derivatives.

Table 5
Antioxidant properties of nicotine derivatives.

Compounds	DPPH assay		2-Deoxyribose assay	
	IC_{50} (μM)	Inhibition at 50 μM (%)	IC_{50}(μM)	Inhibition at 150 μM (%)
[2-NC_5H_3(3-$CONH_2$)Se]$_2$ (**3**)	18.01	93.01 ± 2.69	76.84	84.13 ± 4.78
[2-NC_5H_3(3-CONHPh)Se]$_2$ (**4**)	20.61	91.21 ± 1.9	102.35	63.70 ± 2.32
[2-NC_5H_3(3-CONHPh)SeI] (**7**)	nf	19.93 ± 1.63	nf[a]	31.00 ± 1.34
[2-NC_5H_3(3-CONHpyrimidine)Se]$_2$ (**5**)	nf	27.95 ± 1.72	nf[a]	4.08 ± 2.96
[2-NC_5H_3(3-CONHPh)SeBr] (**6**)	nf	7.82 ± 3.52	nf[a]	13.70 ± 3.1
[2-NC_5H_3(3-COOH)Se]$_2$ (**1**)	nf	ni	nf[a]	2 ± 1.26
[2-NC_5H_3(3-CO)Se–Se] (**2**)	nf	ni	nf[a]	nf[a]
D-Mannitol	–	–	49.80	71.21 ± 3.52
BHT	26.51	86.00 ± 2.3	–	–

The values are the average of three determinations (±SD). nf, not found till 50 μM of test compounds. nf[a], not found till 150 μM of test compounds. ni, no inhibition even at 1:1 concentration of test compound and DPPH.

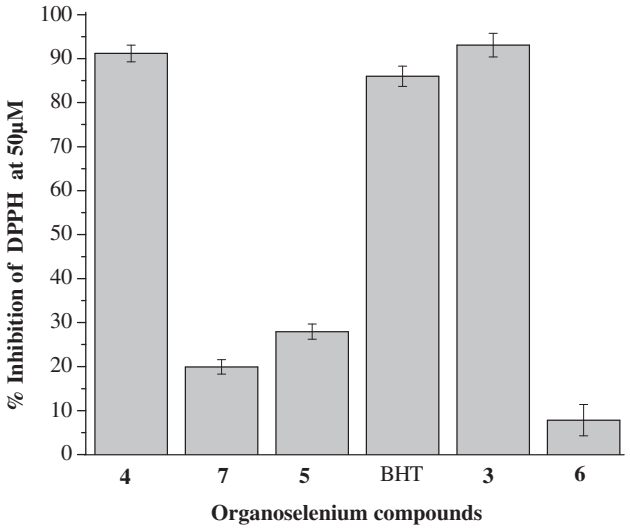


Fig. 6. DPPH radical scavenging ability at highest concentration of 50 μM of nicotinic acid derivative.

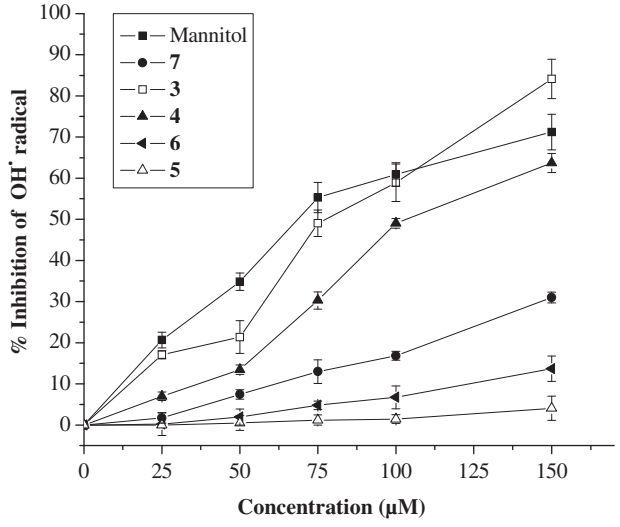


Fig. 7. OH• radical abstraction efficiency of nicotinic acid derivatives by deoxyribose assay.

3.4.2. Deoxyribose assay

Inhibition of the degradation of 2-deoxyribose induced by Fenton-reagent is often used to estimate the hydroxyl radical (•OH) scavenging ability of antioxidants and other organic compounds. The IC_{50} values, i.e. the concentration of selenium compound required to inhibit the degradation by 50% was estimated and compared with standard reference compound, mannitol (positive control) and listed in Table 4 (Fig. 7). The scavenging potential was the highest for D-mannitol followed by **3** and **4** derivatives with IC_{50} values of 49.80, 76.84, 102.35 μM respectively. The behaviour of other derivatives *viz*., **5**–**7** towards radical scavenging is more or less same as in DPPH assay while compounds **1** and **2** do not show any pronounce scavenging abilities.

The results imply that **3** has significantly more hydrogen or electron donating ability which may be due to the presence of free amine. Furthermore absence of amide linkage in derivatives like **1** and cyclic compound **2** showed no significant scavenging ability, clearly demonstrates the essential role of amide linkage in free radical scavenging activities in these screened compounds.

4. Conclusions

In the present study we synthesized new series of nicotinoyl based organoselenium compounds and evaluated their biological activities as GPx mimics and free radical scavenger. Two compounds, **3** and **4** were of great interest as they exhibited potent free radical scavenging ability by DPPH and 2-deoxyribose assays. It is noteworthy that the same were catalytically more efficient than ebselen by means of GPx like activity. From the study it is apparent that GPx and antioxidant activities of nicotinamide based organoselenium compounds depends on the nature of substituent attached to nitrogen atom of amide group. Introduction of either electron donating group like phenyl or electron withdrawing group like pyrimidine to amide linkage has significantly reduced the GPx and free radical scavenging activity. Similarly making selenium-halogen linkage by breaking diselenide bond further decreased both activities. In summary, considering GPx and free radical scavenging abilities, compound **3** may be considered as prominsing candidate.

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Appendix A. Supplementary material

CCDC 853553 [2-NC_5H_3[3-C(O)Se–Se] (**2**) and 853554[2-NC_5H_3(3-CONHPh)Se]$_2$.dmso (**4**.dmso) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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