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PAPER

Synthesis, characterization and structures of 2-(3,5-dimethylpyrazol-1-yl)ethylseleno derivatives and their probable glutathione peroxidase (GPx) like activity†

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A series of 2-(3,5-dimethylpyrazol-1-yl)ethylseleno derivatives has been synthesized. The glutathione peroxidase like catalytic activity of these compounds has been studied in a model system, in which reduction of hydrogen peroxide with dithiothreitol (DTT^{red}), in the presence of an organoselenium compound was investigated by ^{1}H NMR spectroscopy. All these compounds exhibit GPx like catalytic activities and the catalytic reaction proceeds through a selenoxide intermediate, identified by $^{77}Se\{^{1}H\}$ NMR spectroscopy.

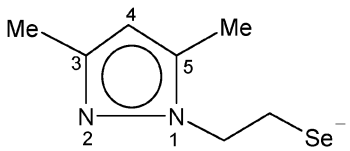
Introduction

Selenium has been recognized as an essential trace element and its deficiency has been linked to many diseases.[1,2] In biological systems, selenium exists in the form of selenoproteins, where it is primarily present in the form of selenocyteine (Sec) which is a higher analogue of cysteine. Selenium in the Sec residue acts as a strong nucleophile in catalytic reactions. Glutathione peroxidase (GPx) is one of the important selenoproteins that protects the cell from peroxides by catalyzing their reduction in the presence of a thiol cofactor, glutathione.[3–5]

Recently selenium compounds have been evaluated as a new class of antioxidants that show reactivity towards reactive oxygen species (ROS) produced during oxidative stress. With the growing importance of selenium in health, over the last decade interest in selenium research has been directed at the design and development of low molecular weight organoselenium compounds that emulate GPx activity. One such synthetic organoselenium compound, ebselen, has been identified as an effective GPx mimic, antioxidant, radioprotector and as an anti-inflammatory agent.[6] The promising pharmacological properties of ebselen have prompted researchers to design newer organoselenium compounds containing heteroatoms like N, O, *etc*.

Accordingly, mono- and di-selenides substituted with functional groups containing heteroatoms have been synthesized and characterized.[7–12] These molecules fall into two broad categories, *viz*. (i) compounds containing a covalent Se–N bond (*e.g.* ebselen) and (ii) molecules containing heteroatoms (N or O) which may either have weak Se···X (X = N, O) non-bonding interactions or are capable of coordinating with selenium at different stages of its catalytic reaction. Selenoethers, like bis(hydroxypropyl)selenide and related derivatives, exhibit high antioxidant activity as GPx mimics.[13] Our recent studies on $(HOOCCH_2CH_2Se)_2$ have shown promising antioxidant activity and low toxicity in mice models.[14–17]

With this background, our group has conceived the synthesis of new organoselenium compounds containing 3,5-dimethylpyrazole fragments (**I**) such that these compounds would exhibit GPx mimicking activity. Results of this work are reported herein.



(I)

Experimental

Materials and methods

Elemental selenium (99.99%), sodium borohydride, superhydride ($LiBEt_3H$), 2-bromoacetic acid, 3-bromopropionic acid, 4-bromobutyric acid and 2-bromoethylamine hydrobromide were purchased from commercial sources (Aldrich/Fluka). Selenium reagents (Li_2Se and Li_2Se_2) were prepared freshly by the reported method.[18] The compounds [$dmpzCH_2CH_2Br$],[19] [2-(4-OTs)C_6H_4CHO],[20] [2-$HOCH_2C_6H_4OTs$],[21] [2-$ClCH_2C_6H_4OTs$][22] and di-2-pyridyldiselenide (py_2Se_2)[23] were prepared according

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† Electronic supplementary information (ESI) available: Synthesis and characterization data of compounds **4–14**, synthesis of $dmpzCH_2CH_2Br$ and other experimental details, ^{1}H NMR, $^{77}Se\{^{1}H\}$ NMR and LC-MS of the 2-(3,5-dimethylpyrazol-1-yl)ethylseleno derivatives (**1–14**) and kinetic analysis data as well as the cif files of the single crystal X-ray diffraction analyses of compounds **3** and **4** are available. CCDC reference numbers 784803 and 784804. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00807a

to known procedures. All reactions were carried out under a nitrogen atmosphere. Solvents were purified and dried by standard procedures[24] and were distilled prior to use. The purity of the organoselenium compounds was tested initially by thin layer chromatography (TLC) followed by column chromatography on silica gel 60/120 mesh size.

Elemental analyses were carried out on a 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 MHz (^{77}Se{^{1}H}). ^{1}H and ^{13}C{^{1}H} NMR chemical shifts were relative to an 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 an 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. IR spectra were recorded on a Bomem MB-102 IR spectrometer.

Synthesis

(dmpzCH$_2$CH$_2$)$_2$Se (1). To a suspension of selenium powder (0.691 g, 8.75 mmol) in THF (75 ml) a slight excess of $LiBEt_3H$ (super hydride) 1 M solution (18.5 ml) in THF, was added carefully at room temperature with magnetic stirring. Vigorous reaction of the selenium with $LiBEt_3H$ resulted in the formation of a white suspension of Li_2Se, to which dmpzCH$_2$CH$_2$Br (3.23 g, 15.9 mmol) was added. The reactants were stirred for a further 6 h. The solvent was evaporated *in vacuo* and the residue was dissolved in distilled water (50 ml). Extraction with diethylether (3 × 50 ml) followed by evaporation of the organic phase *in vacuo* gave a yellow oil which was purified by column chromatography using an ethylacetate–hexane mixture (10 : 90) to yield a pale yellow oil (2.21 g, 85%). NMR spectral data ($CDCl_3$): ^{1}H NMR: δ 2.12, 2.17 (each 3H, s, –C*H*$_3$), 2.76 (2H, t, *J* = 7.0 Hz, –SeC*H*$_2$), 4.07 (2H, t, *J* = 7.0 Hz, –SeCH$_2$C*H*$_2$), 5.70 (1H, s, H-4 dmpz); ^{13}C{^{1}H} NMR: δ 10.9, 13.2 (each s, *Me*), 23.1 ($^1J_{C-Se}$ = 66.0 Hz, Se*C*H$_2$–), 48.7 (*C*H$_2$N), 104.7 (*C*-4 dmpz), 138.8, 147.4 (each s, *C*-3, 5 dmpz); ^{77}Se{^{1}H} NMR: δ 139.6 ppm. MS (IT) *m*/*z*: 327 [M + H]$^+$, 203 [dmpzCH$_2$CH$_2$Se]$^+$.

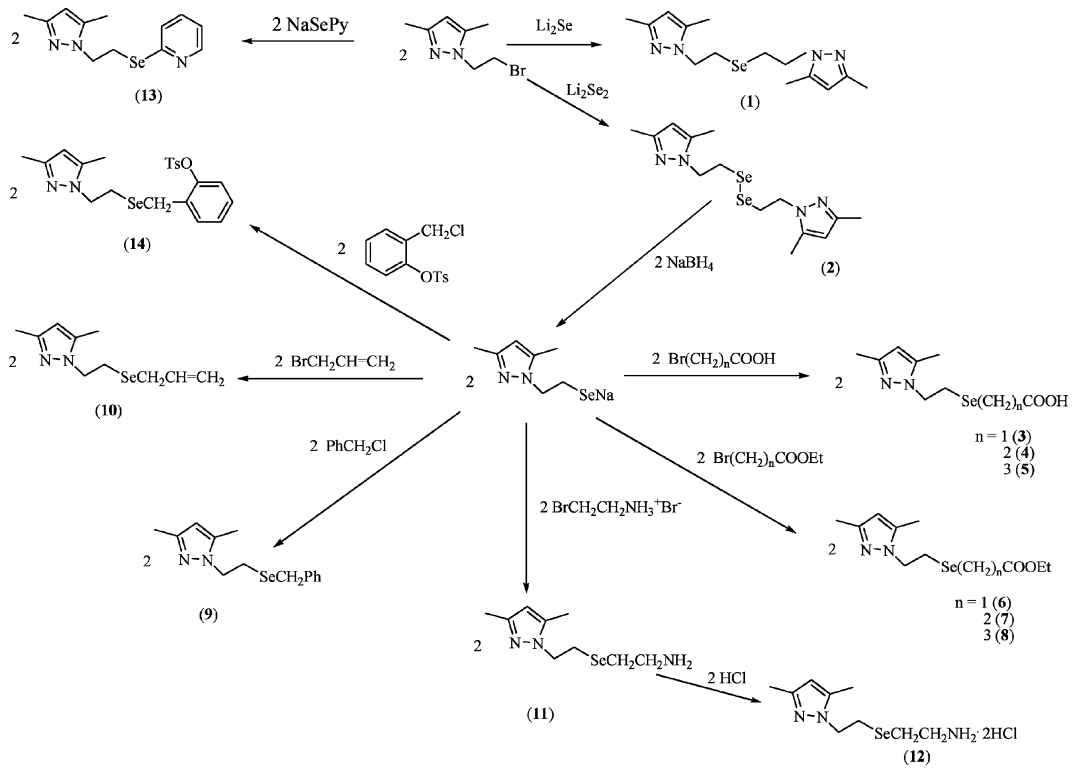
(dmpzCH$_2$CH$_2$Se)$_2$ (2). To a suspension of selenium powder (0.555 g, 7.03 mmol) in THF (75 ml) a $LiBEt_3H$ (super hydride) 1 M solution (7.03 ml, 7.03 mmol) in THF, was added carefully at room temperature with magnetic stirring. Vigorous reaction of the selenium with $LiBEt_3H$ resulted in the formation of a dark brown solution of Li_2Se_2 to which dmpzCH$_2$CH$_2$Br (1.0 g, 4.92 mmol) was added and stirred for a further 4 h. The solvent was evaporated *in vacuo* and the residue was dissolved in distilled water (50 ml). Extraction with diethylether (3 × 50 ml) followed by evaporation of the organic phase *in vacuo* gave a yellow solid which was purified by column chromatography using an ethylacetate–hexane mixture (10 : 90). The yellow solid was recrystallized from diethylether–hexane mixture (50 : 50) at room temperature to yield yellow crystals of the title compound (0.9 g, 90%), m.p. 72–73 °C. Anal. Calcd. for $C_{14}H_{22}N_4Se_2$: Calcd. C, 41.59; H, 5.49; N, 13.86%. Found: C, 41.61; H, 5.45; N, 13.15%. NMR spectral data ($CDCl_3$): ^{1}H NMR: δ 2.19, 2.23 (each 3H, s, –C*H*$_3$), 3.26 (2H, t, *J* = 7.2 Hz, –SeC*H*$_2$), 4.28 (2H, t, *J* = 7.2 Hz, –NC*H*$_2$), 5.77 (1H, s, H-4 dmpz), ^{13}C{^{1}H} NMR: δ 11.1, 13.4 (each s, *Me*), 28.5 ($^1J_{C-Se}$ = 78.0 Hz, Se*C*H$_2$), 48.9 (N*C*H$_2$), 105.0 (*C*-4 dmpz), 139.0, 147.8 (each s, *C*-3, 5 dmpz); ^{77}Se{^{1}H} NMR: δ 293.5 ppm. MS (IT) *m*/*z*: 427 [M + Na]$^+$, 407 [M + H]$^+$, 203 [dmpzCH$_2$CH$_2$Se]$^+$.

dmpzCH$_2$CH$_2$SeCH$_2$COOH (3). To a yellow solution of (dmpzCH$_2$CH$_2$Se)$_2$ (0. 41 g, 1.01 mmol) in 50 ml ethanol, sodium borohydride (0.081 g, 2.13 mmol) was slowly added under a brisk flow of nitrogen at 0 °C. The colorless solution of sodium selenolate obtained was stirred for 30 min and then a solution of 1-bromoacetic acid (0.296 g, 2.13 mmol) in ethanol (15 ml) was added drop wise at room temperature with constant stirring. The reaction mixture was stirred for a further 30 min. The solvent was evaporated *in vacuo*. The white residue was dissolved in distilled water (50 ml) and extracted with diethylether (3 × 50 ml). The ether extract was dried *in vacuo* to give a white solid which was purified by column chromatography with a ethylacetate–hexane mixture (50 : 50) to give a white solid (0.37 g, 70%). It was recrystallized from a ethylacetate–hexane mixture (50 : 50) to yield colorless crystals, m.p. 125–126 °C. Anal. Calcd. for $C_9H_{14}N_2O_2Se_1$: Calcd.: C, 41.39; H, 5.40; N, 10.73%. Found: C, 41.52; H, 5.42; N, 10.90%. IR cm^{-1}: 3585 (υ OH), 1715 (υ CO). NMR spectral data ($CDCl_3$): ^{1}H NMR: δ 2.23, 2.27 (each 3H, s, –C*H*$_3$); 3.09 (2H, s, –SeC*H*$_2$CO), 3.15 (2H, t, *J* = 7.2 Hz, –SeC*H*$_2$), 4.35 (2H, t, *J* = 7.2 Hz, –NC*H*$_2$), 5.84 (1H, s, H-4 dmpz); ^{13}C{^{1}H} NMR: δ 11.0, 12.8 (each s, *Me*), 23.0 ($^1J_{C-Se}$ = 68.0 Hz), 23.8 ($^1J_{C-Se}$ = 69.0 Hz, Se*C*H$_2$), 48.5 (N*C*H$_2$), 105.5 (*C*-4 dmpz), 139.7, 147.8 (each s, *C*-3, 5 dmpz), 174.0 (CO); ^{77}Se{^{1}H} NMR: δ 198.0 ppm. MS (IT) *m*/*z*: 263 [M+H]$^+$, 203 [dmpzCH$_2$CH$_2$Se]$^+$.

The unsymmetrical 3,5-dimethylpyrazole based monoselenide derivatives (Scheme 1) were synthesized (ESI†) by applying the same strategy as adopted for the synthesis of **3**.

X-ray crystallography. Single crystal X-ray data for dmpzCH$_2$CH$_2$Se(CH$_2$)$_n$COOH (*n* = 1 or 2) 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.[25] The structures were solved by direct methods using SHELX-97[26] 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.[27]

Glutathione peroxidase (GPx) activities. The catalytic activity of organoselenium compounds as mimics of GPx was tested by the method reported by Iwaoka *et al.*,[13c,28] in which the reduction of hydrogen peroxide, using DTT^{red} (reduced dithiothreitol) as a thiol cofactor, was monitored by ^{1}H NMR spectroscopy. In a typical experiment DTT^{red} (23.1 mg, 0.15 mmol) and an organoselenium compound (0.015 mmol) as a catalyst were dissolved in CD_3OD (0.5 ml) in a glass vial and the reaction was initiated by addition of freshly standardized H_2O_2 (47.6%) (9.15 µl, 0.15 mmol). At this point the reaction is considered to be at zero time. The progress of the reaction was monitored by ^{1}H NMR spectroscopy. The relative concentration of the thiol (DTT^{red}, δ 3.67 ppm for CH protons) and disulfide (DTT^{ox}, δ 3.49 ppm for CH protons)



Scheme 1 Synthetic routes for preparation of 2-(3,5-dimethylpyrazol-1-yl)ethylseleno derivatives.

was estimated by integrating the respective resonances. The time required for 50% oxidation of the DTT^{red} to DTT^{ox} was calculated, which in turn was a measure of 50% reduction of the H_2O_2 by the cofactor thiol (DTT^{red}). For control, a similar experiment was performed in the absence of a catalyst, *i.e.* organoselenium compound.

Results and discussion

Synthesis

Reactions of 1-(2-bromoethyl)-3,5-dimethylpyrazole with Li_2Se and Li_2Se_2, prepared by the treatment of selenium powder in THF with a stoichiometric amount of superhydride ($LiBEt_3H$) afforded

Table 1 Crystallographic and structural refinement data for $dmpzCH_2CH_2SeCH_2COOH$ (**3**) and $dmpzCH_2CH_2SeCH_2CH_2COOH$ (**4**)

Compound	$dmpzCH_2CH_2SeCH_2COOH$(**3**)	$dmpzCH_2CH_2SeCH_2CH_2COOH$(**4**)
Chemical formula	$C_9H_{14}N_2O_2Se$	$C_{10}H_{16}N_2O_2Se$
Formula weight	261.18	275.21
Color of crystal	colorless	colorless
Crystal size	$0.2 \times 0.1 \times 0.05$	$0.20 \times 0.15 \times 0.10$
Crystal system	Orthorhombic/$Pna2_1$	Monoclinic/P_12_1/n_1
a (Å)	8.370(3)	13.200(5)
b (Å)	11.000(4)	11.169(5)
c (Å)	12.192(3)	7.993(4)
β	90.00	92.12(4)
V (Å^3)	1122.4 (7)	1177.5(9)
Z	4	4
D_c (g cm^{-3})	1.546	1.552
μ(Mo–Kα) mm^{-1}/F (000)	3.324/528	3.172/560
Limiting indices	$-10 \le h \le 6$; $-8 \le k \le 14$; $0 \le l \le 15$	$-9 \le h \le 17$; $0 \le k \le 14$; $-10 \le l \le 10$
θ range for data collection	3.06–27.47	2.93–27.51
No. of reflections collected	1343	2708
No. of independent reflections	788	1595
Data/Restraints/Parameters	1343/1/130	2708/0/140
R indices [$I > 2\sigma(I)$]	$R1 = 0.0400$, $wR2 = 0.0965$	$R1 = 0.0372$, $wR2 = 0.0775$
R indices (all data):	$R1 = 0.1054$, $wR2 = 0.1178$	$R1 = 0.1006$, $wR2 = 0.0977$
$(\Delta/\sigma)_{max}$	0.000	0.000
$(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$	0.447e Å^{-3}, –0.371e Å^{-3}	0.436e Å^{-3}, –0.415e Å^{-3}
Goodness-of-fit on F^2	0.984	1.000

mono-, $(dmpzCH_2CH_2)_2Se$ (**1**) and di-, $(dmpzCH_2CH_2Se)_2$ (**2**) selenides respectively in good yields. The reductive cleavage of the Se–Se bond in the latter (**2**) with a methanolic solution of sodium borohydride gave $dmpzCH_2CH_2SeNa$ which was treated *in situ* with a variety of organic halo compounds yielding a series of asymmetric monoselenides (**3–14**) (Scheme 1). The $dmpzCH_2CH_2Sepy$ (**13**) was synthesized by a reaction between pySeNa and $dmpzCH_2CH_2Br$ in ethanol. All the compounds were purified by column chromatography using ethylacetate–hexane mixtures as an eluent and were characterized by elemental analysis mass and NMR (^1H, $^{13}C\{^1H\}$, $^{77}Se\{^1H\}$) spectroscopies. All the compounds are air and moisture stable and are soluble in polar organic solvents like methanol, ethylacetate, chloroform, *etc.*

Molecular structures

The crystal and molecular structures of $dmpzCH_2CH_2Se(CH_2)_nCOOH$ (n = 1 (**3**) and 2 (**4**) were established by single crystal X-ray diffraction analyses. Selected bond lengths and angles are given in Table 2, while ORTEP drawings with crystallographic numbering scheme are shown in Fig. 1 and 2. The Se–C distance associated with the $dmpzCH_2CH_2$ fragment is slightly shorter than the one connected with the $(CH_2)_nCOOH$ moiety. The two Se–C distances (~1.95 Å) in the two molecules are, however, within the range reported for several aliphatic selenoethers.[29–32] The C–Se–C angles (~98°) in the two molecules are similar and represent a 'V'-shaped configuration around selenium atom. The observed angles are in the range reported for RR′Se compounds (*e.g.*, Me_2Se (96.48 (8)°,[33] $Se(CH_2COOH)_2$ (98.17 (7)°,[29] $Se(CH_2CH_2COOH)_2$ (96.48 (8)°,[34] $pySeCH_2COOH$ (99.67 (9)°[32]).

Table 2 Selected bond lengths (Å) and bond angles (°) for $dmpzCH_2CH_2Se(CH_2)_nCOOH$[$n$ = 1 (**3**) and 2 (**4**]

	$dmpzCH_2CH_2$-$SeCH_2COOH$(**3**)	$dmpzCH_2CH_2$-$SeCH_2CH_2COOH$(**4**)
Bond lengths		
Se(1)–C(1)	1.944(8)	1.944(4)
Se(1)–C(8)	1.956(9)	1.952(4)
C(1)–C(2)	1.473(9)	1.503(6)
C(2)–N(1)	1.468(8)	1.461(4)
N(1)–N(2)	1.356(9)	1.358(4)
N(1)–C(3)	1.361(10)	1.356(5)
N(2)–C(5)	1.347(12)	1.336(5)
C(8)–C(9)	1.480(12)	1.512(5)
C(9)–O(1)	1.206(12)	—
C(9)–O(2)	1.328(11)	—
C(9)–C(10)	—	1.506(6)
C(10)–O(1)	—	1.197(5)
C(10)–O(2)	—	1.315(5)
Bond angles		
C(1)–Se(1)–C(8)	98.0(4)	97.90(18)
Se(1)–C(1)–C(2)	112.9(5)	113.6(3)
C(1)–C(2)–N(1)	113.5(6)	111.6(3)
C(2)–N(1)–C(3)	127.4(9)	127.9(3)
C(2)–N(1)–N(2)	120.2(9)	119.8(3)
N(2)–N(1)–C(3)	112.2(7)	111.9(3)
N(1)–N(2)–C(5)	103.9(9)	105.2(3)
Se(1)–C(8)–C(9)	111.3(6)	109.4(3)
C(8)–C(9)–O(1)	122.7(9)	—
C(8)–C(9)–O(2)	112.9(9)	—
O(1)–C(9)–O(2)	124.4(9)	—
C(9)–O(2)–H(2)	109.5	—
C(8)–C(9)–C(10)	—	112.4(3)
C(9)–C(10)–O(1)	—	124.5(4)
C(9)–C(10)–O(2)	—	112.5(4)
O(1)–C(10)–O(2)	—	123.0(4)
C(10)–O(2)–H(2)	—	109.5

Both **3** and **4** are associated through hydrogen bonding. In both the molecules the hydroxyl proton makes a bond with the pyrazolyl nitrogen (N(2)) (~1.74 Å) of the adjacent molecule rather than the carbonyl oxygen atom. In **3** the hydrogen bonding results in an infinite zigzag chain while such bonding in **4** leads to dimerization. Organoselenium compounds containing a terminal carboxylic acid group show various degrees of association through hydrogen bond interactions. The four parallel hydrogen bonds in $Se(CH_2COOH)_2$ result in a dimeric structure.[29] In contrast the higher homologue $Se(CH_2CH_2COOH)_2$ adopts an infinite chain structure formed by hydrogen bonds between the terminal carboxylic acid groups.[34] A similar infinite zigzag chain is formed in $pySeCH_2COOH$ but with a different mode of hydrogen bonding.[32] In this structure, the pyridyl nitrogen of one unit is hydrogen bonded with the carboxyl group of another molecule. The N(2)···Se(1) distances in **3** and **4** are 4.99 and 5.03 Å, respectively which are much longer than the sum of their van der Waals radii (3.5 Å) indicating the absence of any non-covalent interactions.

Catalytic properties as mimics of GPx

For evaluating GPx like activity, the reaction was performed in CD_3OD by ^1H NMR spectroscopy as reported by Iwaoka *et al.*[28] In the ^1H NMR spectra, the resonances at δ = 2.63, 3.67 ppm, due to DTT^{red}, decreased with a concomitant increase of the signals at δ = 2.87, 3.03, 3.49 ppm, due to DTT^{ox}, with reaction time. The time required to convert DTT^{red} to DTT^{ox} by 50% (t_{50}) indicated the catalytic efficacy of the organoselenium compounds. For $dmpzCH_2CH_2SeCH_2CH_2NH_2{\cdot}2HCl$ (**12**) (0.015 mmol), when used as a catalyst, the oxidation of DTT^{red} was 50% completed within 103 min (t_{50} = 103 min). The best activity was found when $dmpzCH_2CH_2SeCH_2CH_2NH_2$ (**11**) was used as a catalyst at a very low concentration, 0.0016 mmol, where the time required for 50% conversion of DTT^{red} was found to be 12 min. The comparison of the GPx mimicking capacities of the tested organoselenium compounds is shown in Fig. 3. The t_{50} values estimated from these plots for various organoselenium compounds are summarized in Table 3. From these results, it is evident that **11** is the most active organoselenium compound in reducing hydrogen peroxide, with their relative activities in the order of **11** > **12** > **5** > **4** > **1**> **13** > **3** > **2**. The high activity of **11** and **12** in methanol could be due to the presence of an amino group which either acts as a good base catalyst for the GPx reaction illustrated in Scheme 2 or the basicity produced by amino groups in the reaction solution may facilitate the easy conversion of DTT^{red} to DTT^{ox}. Although non-bonding interactions between N(2) of the dmpz and selenium are not observed, such interactions may exist either in the intermediate or in selenoxide, which may possibly stabilize the intermediate, thereby inducing GPx like activity.

The redox reaction shown in Scheme 2 is proposed to proceed through the intermediacy of selenoxide formation.[28] Since similar reaction intermediates are expected to be involved in the GPx activity of our compounds, the reactions were followed by $^{77}Se\{^1H\}$

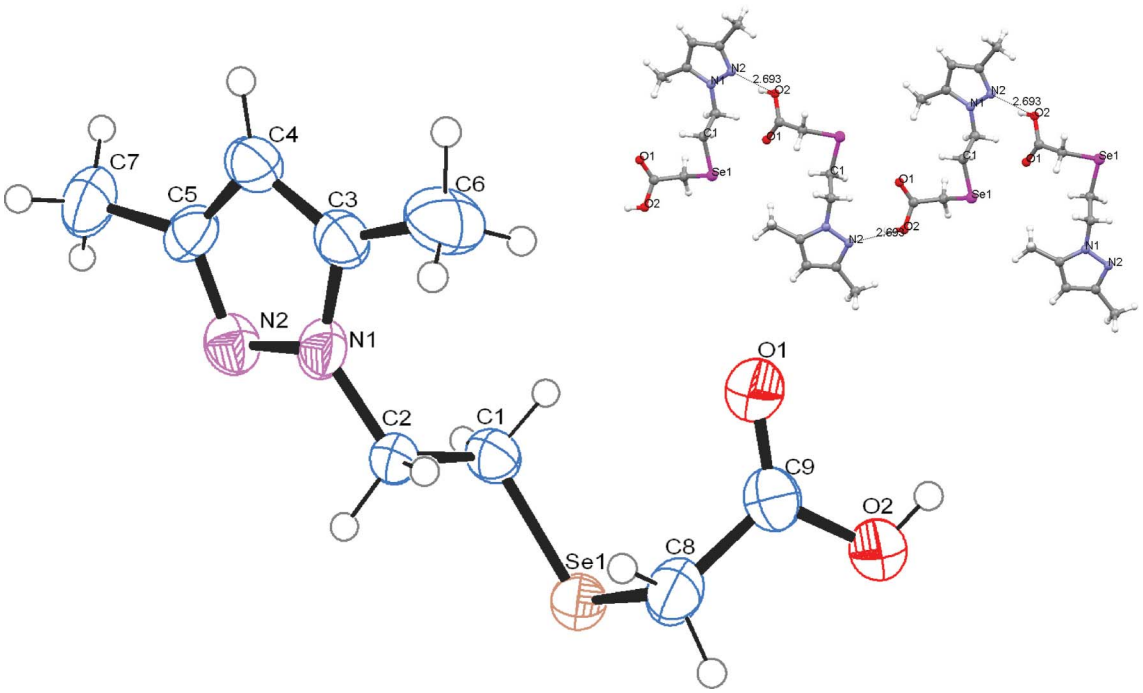


Fig. 1 ORTEP diagram of dmpz$CH_2CH_2SeCH_2COOH$ (**3**) and the inset shows the hydrogen bonding exhibited in the molecule.

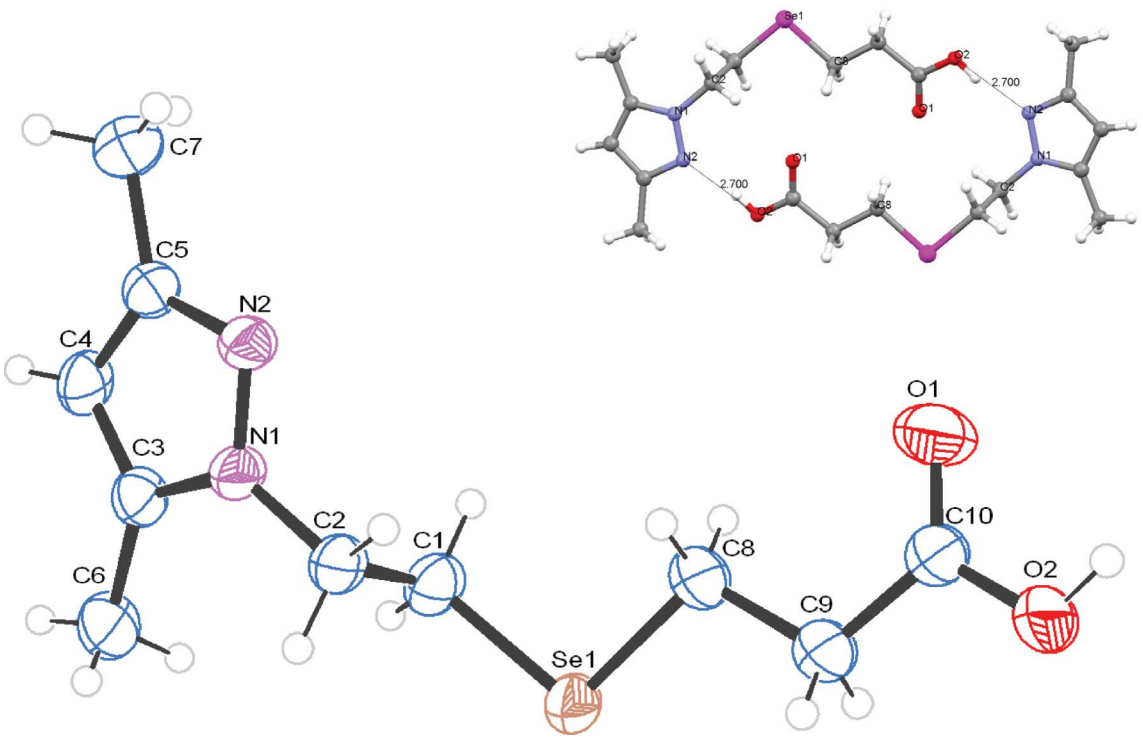


Fig. 2 ORTEP diagram of dmpz$CH_2CH_2SeCH_2CH_2COOH$ (**4**) and the inset shows the hydrogen bonding exhibited in the molecule.

NMR spectroscopy. The chemical shift values for some selected selenoxides of 2-(3,5-dimethylpyrazol-1-yl)ethylseleno compounds are given in Table 4. As is evident from Fig. 4 that the $^{77}Se\{^1H\}$ NMR resonance in D_2O for **12** ($\delta = 119.7$ ppm) is highly deshielded on treatment with one mole equivalent of H_2O_2, indicating the formation of the corresponding selenoxide ($\delta = 816.0$ ppm). The latter signal disappeared with a concomitant appearance of the signal for **12** (δ = 119.7 ppm) on treating the solution with DTT^{red}.

Conclusions

A series of 2-(3,5-dimethylpyrazol-1-yl)ethylseleno derivatives having N atoms in proximity to selenium have been synthesized,

Table 3 Comparative data of GPx-like catalytic activities of organoselenium compounds

Compound		t_{50} in min (by ^{1}H NMR in CD_3OD)
Blank	—	> 300
$(dmpzCH_2CH_2)_2Se$	(**1**)	> 300
$(dmpzCH_2CH_2Se)_2$	(**2**)	> 300
$dmpzCH_2CH_2SeCH_2COOH$	(**3**)	> 300
$dmpzCH_2CH_2SeCH_2CH_2COOH$	(**4**)	160
$dmpzCH_2CH_2SeCH_2CH_2CH_2COOH$	(**5**)	154
$dmpzCH_2CH_2SeCH_2CH_2NH_2$	(**11**)	12[a]
$dmpzCH_2CH_2SeCH_2CH_2NH_2{\cdot}2HCl$	(**12**)	103
$dmpzCH_2CH_2SePy$	(**13**)	> 300

[a] Concentration of (**11**): 0.0016 mmol

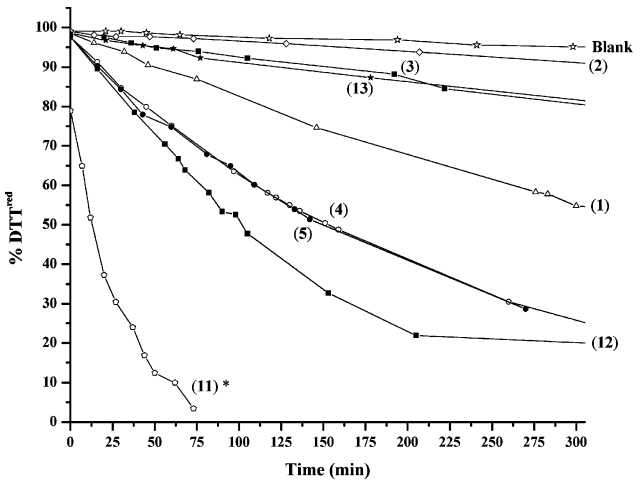
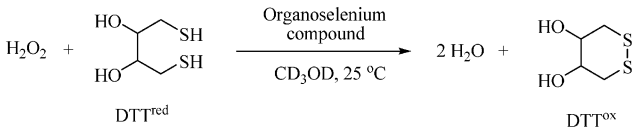


Fig. 3 Percentages of residual DTT^{red} as a function of the reaction time in the oxidation of DTT^{red} with H_2O_2 in the presence of organoselenium catalysts in CD_3OD. Reaction conditions: $[DTT^{red}]_0 = [H_2O_2]_0 = 0.15$ mmol and [selenide] = 0.015 mmol, at 25 °C. *Concentration of (**11**) = 0.0016 mmol.



Scheme 2 Reduction of H_2O_2 with DTT^{red} catalyzed by organoselenium compounds.

purified and characterized. These compounds showed promising GPx activity. The GPx mimicking reactions proceed through the intermediacy of selenoxide formation. It is also evident that in

Table 4 $^{77}Se\{^1H\}$ NMR spectral data for selenoxides of 2-(3,5-dimethylpyrazol-1-yl)ethylselenoxides in D_2O

Compound	$^{77}Se\{^1H\}$ NMR(δ in ppm)
$(dmpzCH_2CH_2)_2SeO$	850.8
$dmpzCH_2CH_2Se(O)CH_2COOH$	802.6
$dmpzCH_2CH_2Se(O)CH_2CH_2COOH$	815.3
$dmpzCH_2CH_2Se(O)CH_2CH_2CH_2COOH$	846.2
$dmpzCH_2CH_2Se(O)CH_2CH_2NH_2$	867.0[a]
$dmpzCH_2CH_2Se(O)CH_2CH_2NH_2{\cdot}2HCl$	816.0

[a] in $CDCl_3$

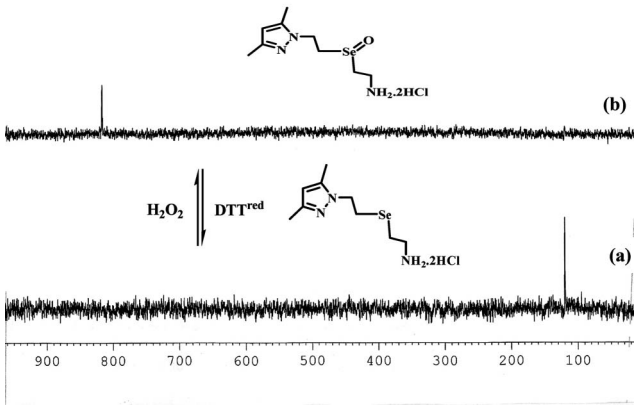


Fig. 4 $^{77}Se\{^1H\}$ NMR spectra (in D_2O) of (a) $dmpzCH_2CH_2SeCH_2CH_2NH_2{\cdot}2HCl$ (**12**) and (b) its oxidation with H_2O_2 to the corresponding selenoxide.

monoselenides, substituted with functional groups like –COOH and $–NH_2$ groups, the GPx mimicking activity increases because of their inductive effect, which facilitates selenoxide formation. In addition, these functionalities enhance solubility in protic solvents.

Supplementary data

Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 784803 ($dmpzCH_2CH_2SeCH_2COOH$) and 784804 ($dmpzCH_2CH_2SeCH_2CH_2COOH$). Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (int. code) +44 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk].

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