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One-pot synthesis of phenylseleno N-acetyl α-amino acids: Supra-molecular self-assembling in organoselenium compounds

C. Parashiva Prabhu [a], Prasad P. Phadnis [a], Amey Wadawale [a], K. Indira Priyadarsini [b], Vimal K. Jain [a,*]

[a] Chemistry Division, Bhabha Atomic Research Centre, Trombay, Mumbai 400 085, India
[b] Radiation and Photochemistry Division, Bhabha Atomic Research Centre, Trombay, Mumbai 400 085, India

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ABSTRACT

A convenient one-pot synthesis of phenylseleno N-acetyl α-amino acids, $PhSeCH_2C(O)NHC(R)COOH$ (R = H (**1**), Me (**2**), $PhCH_2$ (**3**), $4\text{-}HOC_6H_4CH_2$ (**4**) and CH_2OH (**5**)) is reported. These compounds have been characterized by microanalyses, UV–Vis, IR and NMR (^1H, ^{13}C, ^{77}Se) spectroscopy. The molecular structures of $[PhSeCH_2CONHCH_2COOH]$ (**1**), $[PhSeCH_2CONHCH(CH_2C_6H_4OH\text{-}4)COOH]$ (**4**) and $[PhSeCH_2CONHCH(CH_2OH)COOH]$ (**5**) have been established by X-ray diffraction analyses. These compounds are associated in the solid state through hydrogen bonding to give supra-molecular self-assembled structures. Free radical scavenging activity of these compounds has also been evaluated by DPPH assay.

1. Introduction

The chemistry of organoselenium compounds has been a subject of growing interest due to their applications in diverse areas. These include ligands in coordination chemistry [1,2], organic synthesis [3,4], catalysis [5], materials science [6] and biology [7,8]. Inspired by the importance of natural selenoenzymes, which have selenocysteine at their active site, numerous organoselenium compounds have been synthesized mimicking functions exhibited by natural selenoenzymes like glutathione peroxidase (GPx) [8]. Such compounds quite often possess non-bonded intra-molecular Se—X (X = N, O, S) interactions. Some of these synthetic mimics have been designed by incorporating selenium in biologically relevant molecules. Thus selenosugars [9–11], selenopeptides [12,13], selenoglutathione [14] and selenium based nicotinamide derivatives [15] have been prepared.

Supramolecular self-assembly of molecules is of great significance in biology, medicine, drug delivery and materials science [16–18]. Several bio-ensembles, enzymology, molecular devices have been conceptualized based on supramolecular chemical approach [19]. One of the strategies to design supramolecular assemblies exploits non-covalent molecular interactions such as hydrogen bonding, aromatic π–π stacking, *etc.* [20]. Thus compounds containing amino, hydroxyl, carboxylic acid groups can lead to repetitive hydrogen bonding (N—H—O, O—H—O, O—H—N, *etc.*) with neighboring molecules to create supramolecular assemblies. Low valent chalcogen compounds have been known to self-assemble to form columnar-stacks [21]. For instance selenium containing Schiff bases (*e.g.*, $(PhN{=}CHC_6H_4Se)_2$ [22]) and selenium based calixarine (*e.g.*, selenacalix [3]triazine [23]) exhibit supramolecular assemblies. Supramolecular assemblies stabilized by Se(lone pair)…π (aryl) interactions have been reviewed recently [24].

N-acetyl α-amino acids are another important family of biomolecules and constituents of proteins and peptides [25,26] and have the ability to form a variety of supramolecular structures. These derivatives are potential drug molecules. For example, captopril, a derivative of L-proline, is a hypotensive drug [27] while N-acetyl cysteine is used as a mucolytic agent and also used as an antidote for paracetamol toxicity [28]. In development of antioxidants from organoselnium compounds, we have synthesized and characterized organoselnium compounds containing N-acetyl amino acids and have studied their supramolecular structures by single crystal X-ray crystallography. The results of this work are reported herein.

2. Materials and methods

Elemental selenium (99.99%), diphenyl diselenide, sodium borohydride, chloroacetyl chloride, 1,1-diphenyl-2-picryl hydrazyl

* Corresponding author. Tel.: +91 22 2559 5095; fax: +91 22 2550 5151.
E-mail addresses: kindira@barc.gov.in (K.I. Priyadarsini), jainvk@barc.gov.in (V.K. Jain).

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(DPPH), butylated hydroxytoluene (BHT), HPLC grade methanol were obtained from commercial sources (Sigma/Aldrich). Amino acids were obtained from local suppliers and were of analytical grade. Sodium phenylselenolate was prepared by reduction of diphenyl diselenide with stoichiometric quantity of sodium borohydride in ethanol under a nitrogen atmosphere as a colorless solution [29]. All the reactions were carried out under a nitrogen atmosphere. The purity of organoselenium compounds was initially tested by thin layer chromatography and compounds were subsequently purified by column chromatography on a 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 {^{1}H}) and 57.25 MHz (^{77}Se {^{1}H}). ^{1}H and ^{13}C {^{1}H} NMR chemical shifts were relative to internal dmso peak ($\delta = 2.49$ ppm for ^{1}H and $\delta = 39.5$ 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).

2.1. Synthesis

2.1.1. Preparation of [($PhSeCH_2CONHCH_2COOH$] (**1**)

To a clear solution of glycine (2.0 g, 26.6 mmol) in distilled water (40 ml) was added sodium bicarbonate (6.7 g, 79.8 mmol) and stirred for 15 min and cooled to 0–5 °C. To this solution chloroacetyl chloride (2.97 g (2.11 ml), 26.3 mmol) was added drop wise and stirred for 1 h. This solution was mixed to an ice cold sodium phenylselenolate (prepared by adding sodium borohydride (1.0 g, 26.3 mmol) to an ice cold ethanol (20 ml) solution of diphenyl diselenide (4.15 g, 13.3 mmol) under a nitrogen atmosphere) and the contents were stirred for 2 h at room temperature. The solvents were evaporated *in-vacuo* to give a white precipitate which was suspended in water (50 ml) and acidified to pH 6 followed by extraction with chloroform (30 ml × 5). The combined organic fractions were washed with distilled water and the organic layer was dried over sodium sulfate and concentrated *in-vacuo*. The crude residue was column chromatographed using 30:70 ethyl acetate and hexane mixture, which on slow evaporation gave colorless crystals of the title compound (yield 4.67 g, 65%), m.p. 139–141 °C. Anal. for $C_{10}H_{11}NO_3Se$, Calcd: C, 44.13; H, 4.07; N, 5.15%; Found: C, 44.26; H, 4.41; N, 5.10%. UV–Vis (in MeOH) (λ_{max} in nm): 235, 271. IR in KBr (υ cm^{-1}): 3325 (COOH), 1715 (CONH), 1590, 1550. ^{1}H NMR (dmso-d_6) δ: 3.64 (s, $SeCH_2$, 2H); 3.76 (d, 6 Hz, $NHCH_2$, 2H); . 7.28 (m, Ph, 2H); 7.53 (d, 8.4 Hz, Ph, 2H); 8.47 (t, 5.4 Hz, Ph, 1H). ^{13}C {^{1}H} NMR (dmso-d_6) δ: 28.8 ($SeCH_2$; J(^{77}Se–^{13}C) = 65 Hz); 41.0 ($NHCH_2$), 126.8 (Ph), 129.2, 130.5 (Se-Ph), 131.3, 169.5 (CONH), 171.2 (COOH); ^{77}Se {^{1}H} NMR (dmso-d_6) δ: 304 ppm.

2.1.2. Preparation of [$PhSeCH_2CONHCH(Me)COOH$] (**2**)

Prepared similar to **1** using alanine (1.5 g, 16.8 mmol), sodium bicarbonate (4.24 g, 50.5 mmol) and chloroacetyl chloride (1.83 ml, 16.2 mmol) followed by treatment with sodium phenylselenolate, (sodium borohydride (640 mg, 16.8 mmol) in ice cold ethanol (20 ml) and diphenyl diselenide (2.25 g, 7.2 mmol) in ethanol). The product was column chromatographed by using ratios of ethyl acetate and hexane mixture in a sequence 20:80, 30:70, 40:60 (v/v). The fractions eluting in the last ratio was dried to yield a white solid (yield 3.3 g, 79%), m.p. 95–97 °C. Anal. for $C_{11}H_{13}NO_3Se$; Calcd: C, 46.17; H, 4.58; N, 4.89%; Found: C, 45.93; H, 4.76; N, 4.75%. UV–vis (in MeOH) (λ_{max} in nm): 237, 271. IR in KBr (υ cm^{-1}): 3330 (COOH), 1720 (CONH) 1595, 1539. ^{1}H NMR ($CDCl_3$) δ: 1.34 (d, 7.2 Hz, $CHCH_3$, 3H); 3.56 (s, $SeCH_2$, 2H); 4.51 (m, 7.2 Hz, NHCH, 1H); 6.98 (d, 7.1 Hz, Ph, 1H); 7.27 (m, 8.1 Hz, Ph, 2H); 7.52 (m, Ph, 2H); ^{13}C {^{1}H} NMR (dmso-d_6) δ: 17.3 (CH_3), 28.9 ($SeCH_2$, J(^{77}Se–^{13}C) = 66 Hz), 47.9 ($NHCH_2$), 126.9 (Ph), 129.2 (Ph), 130.5 (Ph-Se), 131.5 (Ph), 168.9 (CONH), 174.1 (COOH); ^{77}Se {^{1}H} NMR (dmso-d_6) δ: 306 ppm.

2.1.3. Preparation of [$PhSeCH_2CONHCH(CH_2Ph)COOH$] (**3**)

Prepared similar to **1** using phenyl alanine (2.4 g, 14.5 mmol), sodium bicarbonate (3.65 g, 43.5 mmol) and chloroacetyl chloride (1.97 g, 17.5 mmol) followed by treatment with sodium phenylselenolate (sodium borohydride (540 mg, 14.2 mmol) and diphenyl diselenide (2.26 g, 7.2 mmol) in ethanol). The product was column chromatographed by using 30:70, 40:60 ratios of ethyl acetate and hexane mixture. The faction eluting with 40:60 ratio on concentration afforded a pale yellow powder of the title compound (yield 4.8 g, 91%), m.p. 156–158 °C. Anal. for $C_{17}H_{17}NO_3Se$; Calcd: C, 56.36; H, 4.73; N, 3.87%. Found: C, 56.04; H, 4.17; N, 3.18%. UV–Vis (in MeOH) (λ_{max} in nm): 237, 275. IR in KBr (υ cm^{-1}): 3290 (COOH), 1705 (CONH), 1600, 1555. ^{1}H NMR (dmso-d_6) δ: 2.82 (each, m, CH_2Ph); 2.88 (m, NHCH, 1H); 3.07 (br, OH/NH); 3.59 (s, $SeCH_2$); 4.44 (m, CH, 2H); 7.27 (m, Ph, 8H); 7.47 (d, 7.8 Hz, Ph, 2H); 8.47 (d, 7.8 Hz, Ph, 1H). ^{13}C {^{1}H} NMR (dmso-d_6) δ: 28.7 ($SeCH_2$, J(^{77}Se–^{13}C) = 66 Hz), 36.6 (NHCH), 53.7 ($PhCH_2$), 126.5 (Ph), 126.6 (Ph), 128.2 (Ph), 129.1 (Ph), 130.5 (SePh), 131.1 (Ph), 137.3 (Ph), 168.9 (CONH), 172.7 (COOH). ^{77}Se {^{1}H} NMR (dmso-d_6) δ: 305 ppm.

2.1.4. Preparation of [$PhSeCH_2CONHCH(CH_2C_6H_4OH\text{-}4)COOH$] (**4**)

Prepared similar to **1** using tyrosine (1.8 g, 9.9 mmol), sodium bicarbonate (2.49 g, 29.6 mmol) and chloroacetyl chloride (1.83 g, 16.2 mmol) followed by treatment with sodium phenylselenolate (sodium borohydride (370 mg, 9.7 mmol) and diphenyl diselenide (1.54 g, 4.9 mmol) in ethanol). The product was column chromatographed by using ethyl acetate - hexane mixture (40:60 ratio) and recrystallized from ethyl acetate as white crystals (yield 0.8 g, 21%), m.p. 175–178 °C. Anal. for $C_{17}H_{17}NO_4Se$; Calcd: C, 53.98; H, 4.53; N, 3.70%. Found: UV–Vis (in MeOH) (λ_{max} in nm): 216. IR in KBr (υ cm^{-1}): 3185 (COOH), 1750 (CONH), 1590 (COOH). ^{1}H NMR (dmso-d_6) δ: 2.07–2.93 (m, distereotopic, $CH_2C_6H_4OH$); 3.46 (br, NH and COOH); 3.60 (s, $SeCH_2$); 4.30–4.37 (m, CH–COOH); 6.63, 6.99 (each d, 8.4 Hz, C_6H_4); 7.25 (m); 7.47 (m), 8.39 (d, 7.8 Hz) [Ph]; 9.26 (br, C_6H_4OH). ^{13}C {^{1}H} NMR (dmso-d_6) δ: 28.8 ($SeCH_2$, J(^{77}Se–^{13}C) = 66 Hz), 36.1 (NHCH), 54.1 ($CH_2C_6H_4$); 115.0, 127.3, 131.2, 156.0 (C_6H_4OH); 126.7, 127.3, 129.2, 130.1 (Ph); 168.9 (CONH), 172.9 (COOH). ^{77}Se {^{1}H} NMR (dmso-d_6) δ: 303 ppm.

2.1.5. Preparation of [$PhSeCH_2CONHCH(CH_2OH)COOH$] (**5**)

Prepared similar to **1** using serine (3.66 g, 34.8 mmol), sodium bicarbonate (8.77 g, 104.4 mmol), chloroacetyl chloride (3.81 g, 33.7 mmol) and sodium phenylselenolate, (sodium borohydride (1.32 g, 34.8 mmol) and diphenyl diselenide (5.43 g, 17.4 mmol) in ethanol). The product was column chromatographed by using 30:70 of ethyl acetate - hexane mixture followed by concentration to give a white powder which was recrystallized from ethyl acetate - chloroform mixture (30:70) (yield 4.6 g, 43%), m.p. 112–115 °C. Anal. for $C_{11}H_{13}NO_4Se$; Calcd: C, 43.72; H, 4.34; N, 4.64%. Found: C, 43.41; H, 5.11; N, 4.41%. UV–Vis (in MeOH) (λ_{max} in nm): 237, 269. IR in KBr (υ cm^{-1}): 3630 (CH_2OH), 1735 (COOH), 1600 (CONH). ^{1}H NMR (dmso-d_6) δ: 3.56–3.72 (m, CH_2OH, NH/COOH); 3.68 (s, $SeCH_2$); 4.25–4.30 (m, CH); 7.23–7.31 (m), 7.53 (d, 7.8 Hz); 8.36 (d, 7.8 Hz) [Ph]. ^{13}C {^{1}H} NMR (dmso-d_6) δ: 17.3 ($NHCH_3$), 28.8 ($SeCH_2$, J(^{77}Se–^{13}C) = 66 Hz), 47.8 (CH_2OH), 126.8, 129.2, 130.4, 131.4 (Ph), 168.8 (CONH), 174.0 (COOH). ^{77}Se {^{1}H} NMR (dmso-d_6) δ: 303 ppm.

2.1.6. Preparation of [$PhSeCH_2COOH$] (**6**)

An ethanolic solution (10 ml) of iodoacetic acid (1.71 g, 9.1 mmol) was added to a stirred ice cold solution of sodium phenylselenolate (from sodium borohydride (520 mg, 13.6 mmol) and

Table 1
Crystallographic and structural refinement data for [$PhSeCH_2CONHCH_2COOH$] (**1**), [$PhSeCH_2CONHCH(CH_2C_6H_4OH\text{-}4)COOH$] (**4**) and [$PhSeCH_2CONHCH(CH_2OH)COOH$] (**5**).

Compound	[$PhSeCH_2CONHCH_2COOH$] (**1**)	[$PhSeCH_2CONHCH(CH_2C_6H_4OH\text{-}4)$ COOH] (**4**)	[$PhSeCH_2CONHCH(CH_2OH)COOH$] (**5**)
Chemical formula	$C_{10}H_{11}NO_3Se$	$C_{17}H_{17}NO_4Se$	$C_{11}H_{13}NO_4Se$
Formula weight	272.16	378.28	302.18
Crystal size (mm)	0.25 × 0.10 × 0.10	0.30 × 0.20 × 0.20	0.25 × 0.25 × 0.15
Crystal system	Monoclinic/P $2_{1/n}$	Orthorhombic/P 2_1 2_1 2_1	Monoclinic/$P2_1$
a (Å)	8.3290(19)	8.4310(16)	4.8231(12)
b (Å)	10.113(2)	10.4000(17)	19.103(4)
c (Å)	12.970(2)	18.616(3)	6.7574(19)
β	95.000(16)		98.36(2)
V (Å^3)	1088.3(4)	1632.3(5)	616.0(3)
Z	4	4	2
D_c (g/cm^3)	1.661	1.539	1.629
μ(Mo-$K\alpha$) mm^{-1}/F (000)	3.436/544	2.320/768	3.050/304
θ range for data collection	2.56–27.48	2.65–27.58	3.05–27.48
No. of reflections collected	2493	2404	1449
Limiting indices	$-10 \le h \le 10$	$-6 \le h \le 10$	$-6 \le h \le 3$
	$-7 \le k \le 13$	$-13 \le k \le 7$	$-24 \le k \le 0$
	$-9 \le l \le 16$	$-24 \le l \le 0$	$-8 \le l \le 8$
Data/restraints/parameters	2493/0/144	2404/3/217	1449/1/166
R indices [$I > 2\ \sigma\ (I)$]	$R1 = 0.0365$, $wR2 = 0.0629$	$R1 = 0.0415$, $wR2 = 0.1149$	$R1 = 0.0357$, $wR2 = 0.0860$
R indices (all data):	$R1 = 0.\ 0.1488$, $wR2 = 0.0926$	$R1 = 0.1107$, $wR2 = 0.0905$	$R1 = 0.0685$, $wR2 = 0.0819$
Goodness-of-fit on F^2	1.022	1.088	1.096

diphenyl diselenide (1.43 g, 4.5 mmol) in ethanol) under a nitrogen atmosphere. The contents were stirred for 1 h. The solvent was removed *in-vacuo* and the residue was dissolved in water (30 ml) and acidified to pH 6. The product was extracted with ethyl acetate. The solvent was evaporated under vacuum and the residue was column chromatographed by eluting with 40:60 hexane–ethyl acetate to give colorless crystals of **6** (yield 1.3 g, 66%), m.p. 76–79 °C. Anal. for $C_8H_8O_2Se$; Calcd: C, 44.6; H, 3.72%. Found: C, 44.66; H, 3.71%. UV–Vis (in MeOH) (λ_{max} in nm): 243, 275. IR in KBr (υ cm^{-1}): 3365 (COOH), 2930 (Ph), 1630 (CO). ^{1}H NMR ($CDCl_3$) δ: 3.53 (br, 2H); 7.65 (br, Ph, 5H); 11.18 (s, COOH, 1H). ^{13}C {^{1}H} NMR (dmso-d_6) δ: 27.1 ($SeCH_2$, J(^{77}Se–^{13}C) = 69 Hz); 127.9 (Ph), 129.1 (Ph), 133.2 (Ph), 176.6 (COOH). ^{77}Se{^{1}H} NMR (dmso-d_6) δ: 341 ppm.

2.1.7. Preparation of [$PhSeCH_2CONH_2$] (**7**)

Prepared similar to **6** using chloroacetamide (1.0 g, 10.7 mmol) and sodium phenylselenolate (from sodium borohydride (610 mg, 16.1 mmol) and diphenyl diselenide (1.56 g, 5.0 mmol) in ethanol) and recrystallized from ethyl acetate as a white crystalline solid (yield 1.73 g, 80%), m.p. 85–89 °C. Anal. for C_8H_9NOSe; Calcd: C, 44.87; H, 4.21; N, 6.54%. Found: C, 44.69; H, 4.24; N, 6.31%. UV–Vis (in MeOH) (λ_{max} in nm): 240, 271. IR in KBr (υ cm^{-1}): 3365 (NH_2), 1655 (CO). ^{1}H NMR ($CDCl_3$) δ: 3.55 (s, CH_2Se); 3.44 (s, NH_2); 7.10 (br), 7.23–7.56 (m) [Ph]. ^{13}C {^{1}H} NMR (dmso-d_6) δ: 29.2 ($SeCH_2$, J(^{77}Se–^{13}C) = 65); 126.7 (Ph), 129.2 (Ph), 130.6 (SePh), 131.0 (Ph), 171.1 ($CONH_2$). ^{77}Se{^{1}H} NMR (dmso-d_6) δ: 302 ppm.

2.2. DPPH free radical scavenging assay

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

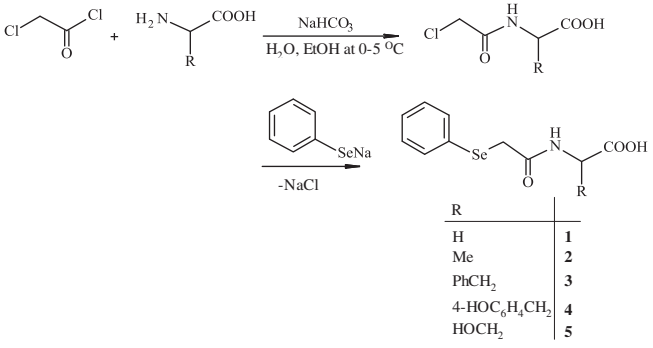
2.3. X-ray crystallography

Single crystal X-ray diffraction data for [$PhSeCH_2CONHCH_2$-COOH] (**1**), [$PhSeCH_2CONHCH(CH_2C_6H_4OH\text{-}4)COOH$] (**4**), [$PhSeCH_2CONHCH(CH_2OH)COOH$] (**5**) 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 [31]. The structures were solved by direct methods using SHELX-97 [32], 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 [33].

3. Results and discussion

3.1. Synthesis

Phenylseleno N-acetyl α-amino acids have been prepared conveniently in one-pot. Various amino acids on treatment with chloroacetyl chloride in the presence of sodium bicarbonate in water gave the corresponding chloro N-acetylated α-amino acids. The latter, without separation, on reaction with NaSePh (obtained by reductive cleavage of Se–Se bond of Ph_2Se_2 with $NaBH_4$ in ethanol) in the same flask yield phenylseleno N-acetyl-α-amino acids (Scheme 1). The basicity (pH ~9) of the reaction mixture avoids protonation of the



Scheme 1.

PhSe to selenol. Use of sodium hydroxide as a base in place of sodium bicarbonate, yields a mixture of both N- and O- acetylated derivatives. There are numerous methods known to synthesize N-acetylated α-amino acids. These include use of dry pyridine [34], applying modified zeolites [35], 1-hydroxy benzotriazole (HO-Bt) or N-hydroxy succinamide (HO-Su) [36], by C-terminal protection [37], acylation in non-conventional medium [38], *etc.*

The electronic spectra displayed two bands at ~ 240 and ~270 nm due to $\pi-\pi^*$ and $n-\pi^*$ transitions, respectively. The IR spectra of these compounds except **5** showed a broad peak in the region 3185–3365 cm^{-1} assignable to COOH group, while for **5** it appeared at 3630 cm^{-1}. The spectra exhibited absorptions in the regions 1705–1750 and 1590–1630 cm^{-1} due to carbonyl stretchings of CONH and COOH groups, respectively.

The ^1H and ^{13}C NMR spectra displayed expected resonances and peak multiplications. The $SeCH_2$ group appeared as a singlet at ~3.60 and ~29.0 ppm in the ^1H and ^{13}C NMR spectra, respectively. The magnitude of $^1J(Se-C)$ of ~66 Hz is in accordance with the values reported for seleno ethers [39]. The carbonyl resonance of the amide group in the ^{13}C NMR spectra appeared at ~169 ppm. The spectra displayed a resonance due to carbonyl carbon of the carboxylic acid group in the region 171.2–176.6 ppm. The ^{77}Se NMR

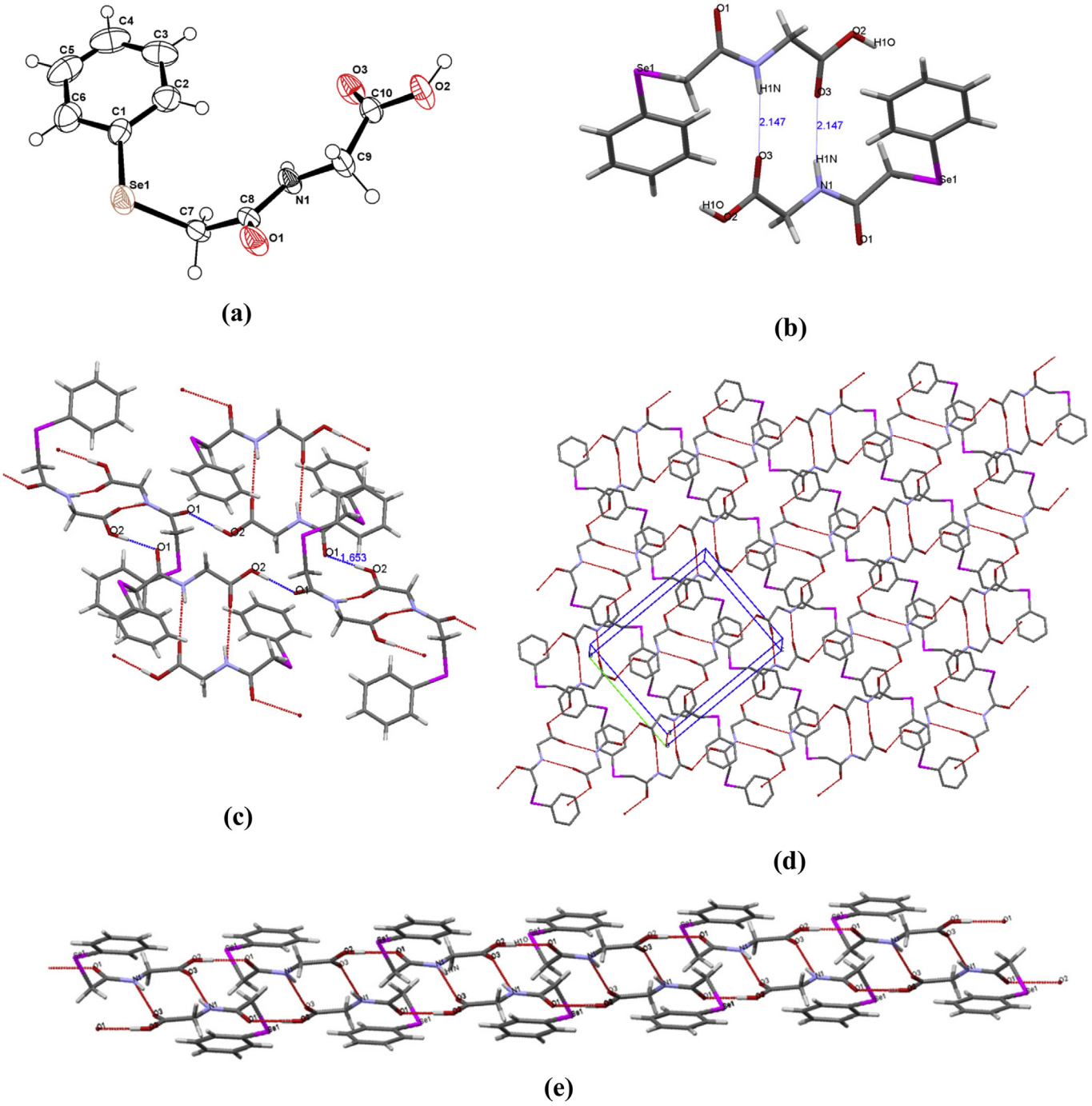


Fig. 1. (a) ORTEP drawing with crystallographic numbering scheme of [$PhSeCH_2CONHCH_2COOH$] (**1**) with 50% thermal ellipsoid probability (b) Hydrogen bonded dimer (c) Hydrogen bonded tetramer (d) packing along *a*-axis (e) packing along 110 axis.

spectra displayed a single resonance ~304 ± 2 ppm which is little influenced by the nature of the amino acid residue.

3.2. Crystallography

The molecular structures of [$PhSeCH_2CONHCH_2COOH$] (**1**), [$PhSeCH_2CONHCH(CH_2C_6H_4OH\text{-}4)COOH$] (**4**) and [$PhSeCH_2CONHCH(CH_2OH)COOH$] (**5**) have been unambiguously established by single crystal X-ray diffraction analysis. ORTEP drawings are given Figs. 1–3 while the selected inter-atomic parameters are given in Tables 2–4. All the three monoselenides adopt a 'V' - shaped configuration around the selenium atom with the C–Se–C angles varying between 98.8(3) and 101.43(3)° and are well within the range reported for several seleno ethers, RSeR' (*e.g.* $Se(CH_2COOH)_2$ 98.17(7)° [40], $pySeCH_2COOH$ (99.67 (9)° [41] and $dmpzC_6H_4SeCH_2COOH$ 101.2(3)° [42]). The Se–C distances are well in agreement with the values reported for organoselenium(II) compounds [40–42]. The Se–C distance associated with the phenyl group is shorter than those connected with the aliphatic carbon atom.

All the molecules are associated through hydrogen bonding involving amide, carbonyl, carboxylic acid and/or alcoholic/phenolic groups to form supra-molecular assemblies. In the case of [$PhSeCH_2CONHCH_2COOH$] (**1**), two neighboring molecules are hydrogen bonded (2.147 Å) to form a dimer through O3 atom of one molecule and N1H of other molecule. Four such dimeric units assemble through hydrogen bonding to form a tetrameric assembly. In the latter, O1 of dimeric unit coordinates to O2H of the carboxylic acid group of a neighboring dimer with O1…HO2 distance of 1.653 Å. These tetrameric units form self-assembled supra-molecular structures through further such hydrogen bonding.

In the case of [$PhSeCH_2CONHCH(CH_2C_6H_4OH\text{-}4)COOH$] (**4**), the molecule forms a hydrogen bonded 3D structure. Hydrogen bonding is seen between the carbonyl group (O1) and carboxylic acid group (O3H) (O1…HO3 = 1.855 Å) of one molecule and phenolic group O4 (O1…HO4 = 1.944 Å) of another molecule. The phenolic group O4 of each molecule is also hydrogen bonded with N1 of amide group (O4…HN1 = 2.252 Å) along with the carbonyl O1 group of two different molecules.

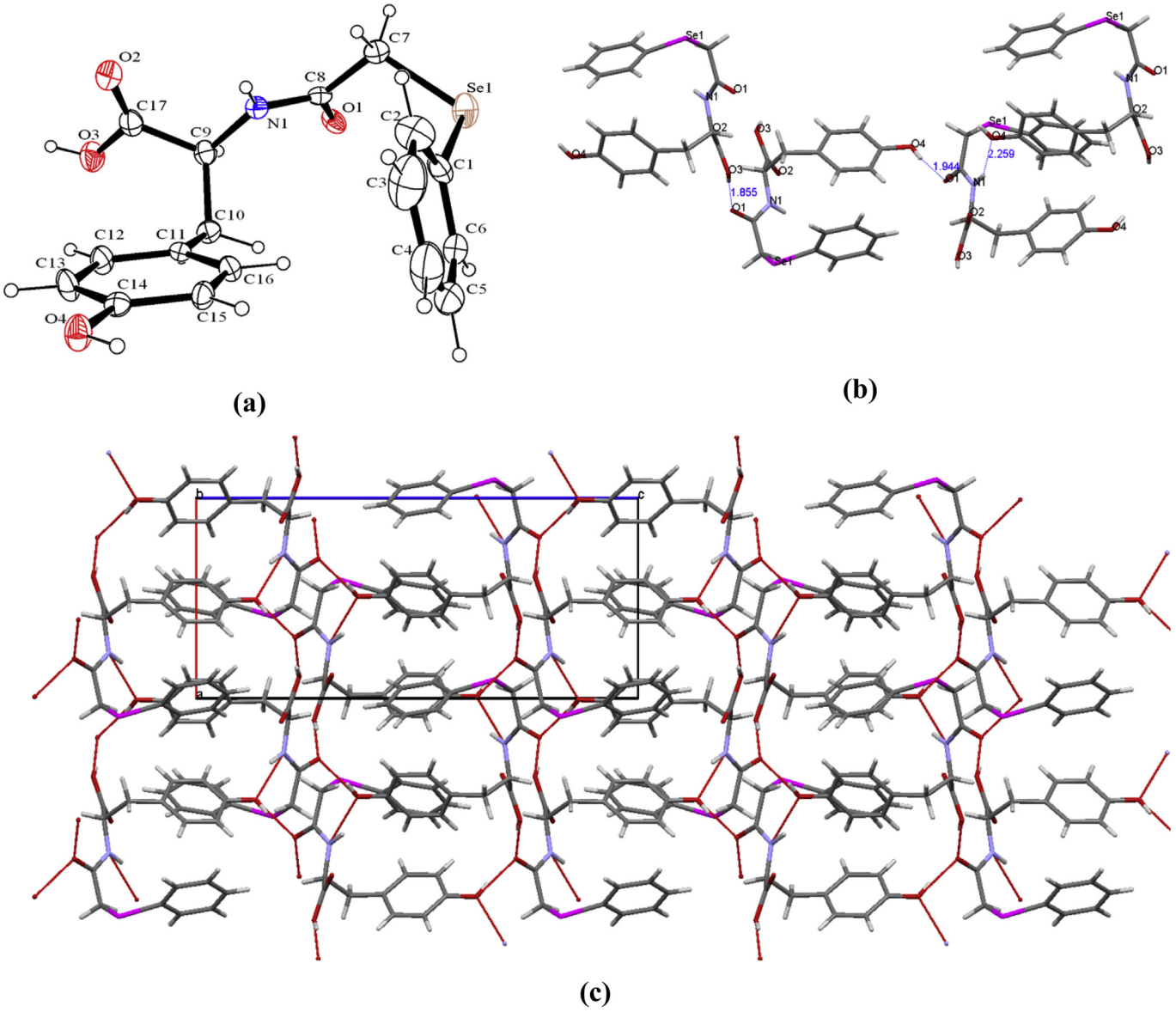


Fig. 2. (a) ORTEP drawing with crystallographic numbering scheme of [$PhSeCH_2CONHCH(CH_2C_6H_4OH\text{-}4)COOH$] (**4**) with 50% thermal ellipsoid probability (b) hydrogen bonding (c) packing view along *c*-axis.

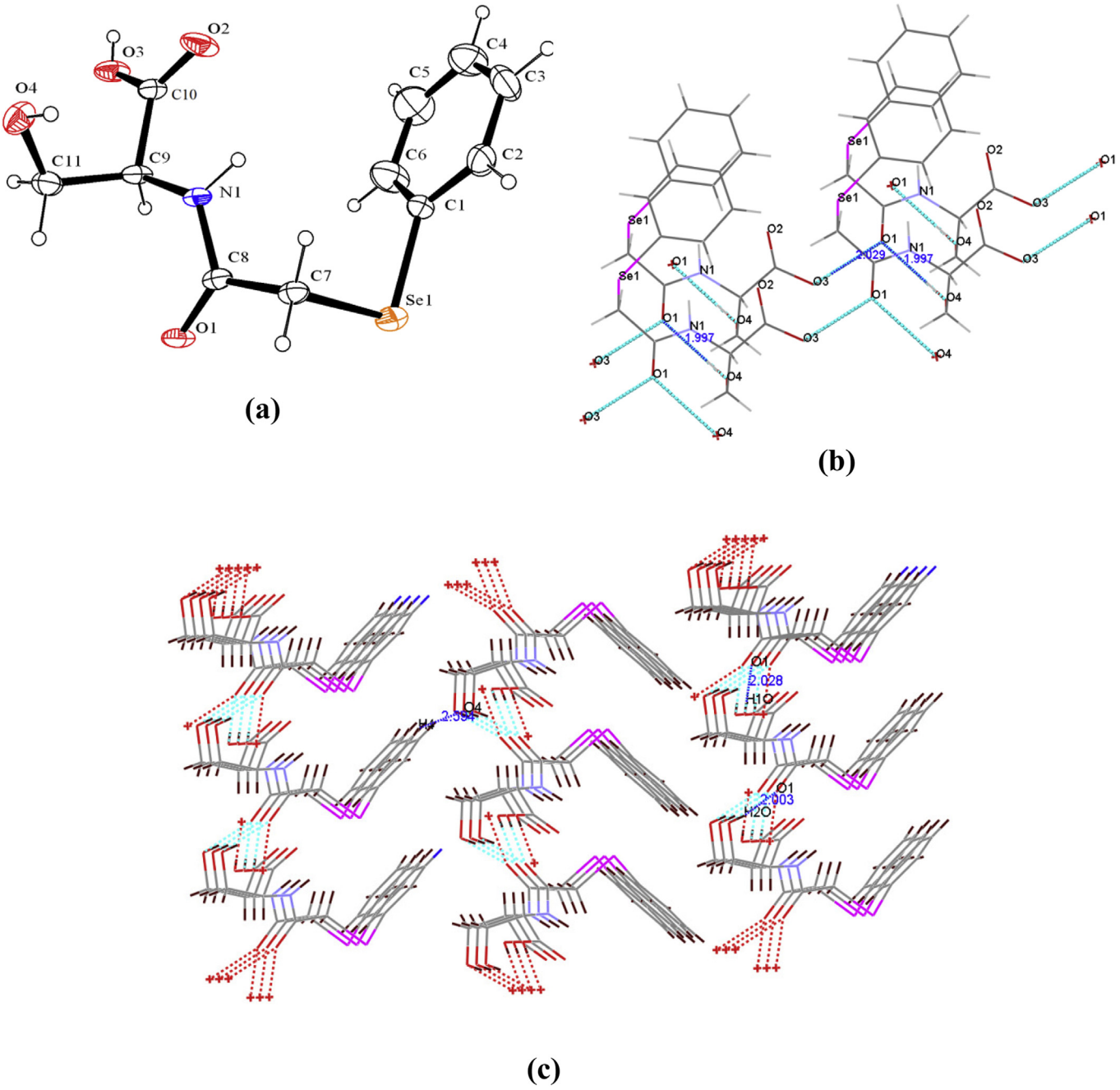


Fig. 3. (a) ORTEP drawing with crystallographic numbering scheme of [$PhSeCH_2CONHCH(CH_2OH)COOH$] (**5**) with 50% thermal ellipsoid probability (b) hydrogen bonding (c) packing view along *a*-axis.

Table 2
Selected bond lengths (Å) and angles (°) for [$PhSeCH_2CONHCH_2COOH$] (**1**).

Se1–C1	1.919(5)	O1–C8	1.236(5)
Se1–C7	1.952(4)	N1–C8	1.338(5)
O3–C10	1.198(5)	N1–C9	1.446(5)
O2–C10	1.309(5)	C10–C9	1.446(5)
C1–Se1–C7	100.85(19)	O1–C8–N1	120.3(4)
C8–C7–Se1	111.2(3)	C7–C8–N1	117.0(4)
O3–C10–O2	125.4(4)	O3–C10–C9	123.9(4)
C7–C8–O1	122.7(4)	O2–C10–C9	110.7(4)

Table 3
Selected bond lengths (Å) and angles (°) for [$PhSeCH_2CONHCH(CH_2C_6H_4OH\text{-}4)COOH$] (**4**).

C1–Se1	1.918(7)	C8–O1	1.242(7)
C7–Se1	1.941(7)	C17–O2	1.198(9)
C8–N1	1.318(8)	C17–O3	1.351(9)
C9–N1	1.462(9)	C14–O4	1.375(7)
C9–C17	1.502(10)		
C1–Se-1 C7	101.4(3)	C8–C7–Se1	111.1(5)
C8–N1–C9	120.0(5)	C7–C8–O1	119.8(7)
O2–C17–O3	124.8(7)	N1–C8–O1	122.3(6)
O2–C17–C9	126.8(7)	N1–C9–C10	112.0(6)
O3–C17–C9	108.4(7)		

Table 4
Selected bond lengths (Å) and angles (°) for [$PhSeCH_2CONHCH(CH_2OH)COOH$] (**5**).

Se1–C1	1.909(6)	O4–C11	1.415(8)
Se1–C7	1.953(6)	O1–C8	1.241(7)
O3–C10	1.300(9)	N1–C8	1.360(7)
O2–C10	1.207(8)	N1–C9	1.454(9)
C1–Se1–C7	98.8(3)	C8–C7–Se1	109.0(4)
O2–C10–O3	124.9(6)	C8–N1–C9	124.6(6)
O2–C10–C9	122.4(6)	O1–C8–C7	123.1(5)
O3–C10–C9	112.7(6)	C9–C11–O4	112.6(6)
O1–C8–N1	121.4(6)		

Table 5
Radical scavenging ability or phenylseleno N-acetyl amino acid derivatives in DPPH assay.

Compound	% protection at 50 μM	IC_{50} (μM)
1	9.3	[a]
2	8.5	[a]
3	9.8	[a]
4	33.5	[a]
5	30.1	[a]
6	11.1	[a]
7	8.2	[a]
BHT	86.3	29.1

[a] IC_{50} value could not be obtained even at max concentration of 50 μM of the test compound against 100 μM DPPH.

In the case of [$PhSeCH_2CONHCH(CH_2OH)COOH$] (**5**) the carbonyl oxygen atom (O1) of one molecule is hydrogen bonded to two different neighboring molecules, one through hydroxyl group (O4H) (O1...HO4 = 2.003 Å) and carboxylic acid group (O3H) of another molecule (O1…HO3 = 2.028 Å). The above hydrogen bonding results in a single two dimensional layer in which molecules are oriented parallel both along the *a*- and *c*-axes. These layers are in turn held together in the crystal lattice with short interaction between O4 from one layer and one of the phenyl hydrogens (C4H) from the adjacent layer (O4…-HC4 = 2.594 Å).

3.3. DPPH scavenging assay

Antioxidant activity of organoselenium compounds *in-vitro* can be evaluated by different methods, like colorimetric methods (DPPH [30]), $ABTS^{+}$ de-colorization [43] and TBARS assay [44]. In the former the characteristic absorption at 517 nm due to DPPH radical decreases on interaction with a radical scavenger and the extent of decrease in absorption determines the scavenging ability of the test compound. This method has been employed for evaluation of antioxidant capacity of phenylseleno N-acetyl α-amino acids using BHT as a positive control. The resulting data on antioxidant activities are given in Table 5. The scavenging effect of the N-acetylated amino acids and control on the DPPH radical decreased in the order of BHT >**4** > **5** > **6** > **3** > **1** > **2** > **7** and was 86.28, 33.5, 30.1, 11.1, 9.8, 9.3, 8.5, 8.2%, respectively for complete scavenging of radicals at 50 μM concentration. Scavenging ability increased by increasing the concentration of the compound thus indicating concentration dependency during the course of activity as given in Fig. 4. The activity of **4** is followed by **5** when compared to remaining derivatives **6**, **3**, **1**, **2**, **7** which are inactive as free radical scavenging could be due to the presence of OH group.

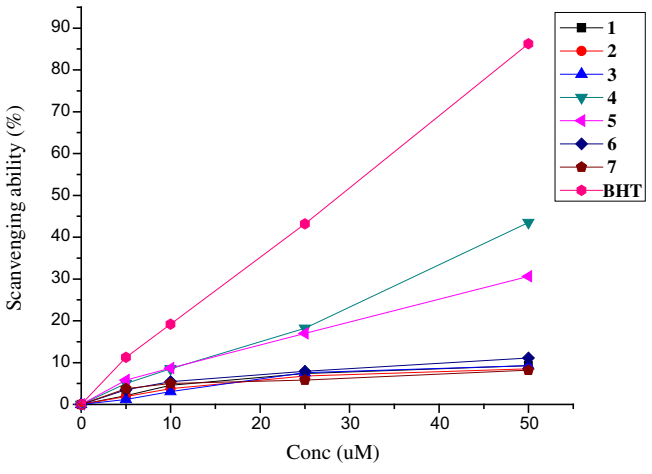


Fig. 4. Radical scavenging activity (%) showed by phenylseleno N-acetyl amino acids against DPPH radical.

4. Conclusions

A convenient one-pot synthesis of phenylseleno N-acetyl α-amino acids has been developed. These compounds are associated in the solid state through hydrogen bonding leading to supramolecular assemblies. A subtle change in the nature of R group on the amino acid fragment results in stabilizing different motifs of secondary structures. These compounds, although, show poor free-radical scavenging activity, their supramolecular assembly can be used in future applications in biology and medicine.

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Appendix A. Supporting Information

CCDC 932338, 932340 and 932339 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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