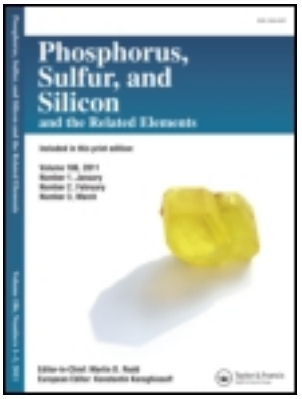

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Synthesis, Characterization, and X-Ray Structures of 2-(3,5-Dimethylpyrazol-1-Yl)Phenyl-Based Organoselenium Compounds and Their Glutathione Peroxidase (Gpx) Like Activity

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Accepted author version posted online: 12 Jul 2012.Published online: 10 Sep 2012.

To cite this article: Ananda S. Hodage, Prasad P. Phadnis, Amey Wadawale, K. I. Priyadarsini & Vimal K. Jain (2012) Synthesis, Characterization, and X-Ray Structures of 2-(3,5-Dimethylpyrazol-1-Yl)Phenyl-Based Organoselenium Compounds and Their Glutathione Peroxidase (Gpx) Like Activity, Phosphorus, Sulfur, and Silicon and the Related Elements, 187:12, 1419-1433, DOI: 10.1080/10426507.2012.686545

To link to this article: http://dx.doi.org/10.1080/10426507.2012.686545

Phosphorus, Sulfur, and Silicon, 187:1419–1433, 2012

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2012.686545

SYNTHESIS, CHARACTERIZATION, AND X-RAY STRUCTURES OF 2-(3,5-DIMETHYLPYRAZOL-1-YL)PHENYL-BASED ORGANOSELENIUM COMPOUNDS AND THEIR GLUTATHIONE PEROXIDASE (GP*x*) LIKE ACTIVITY

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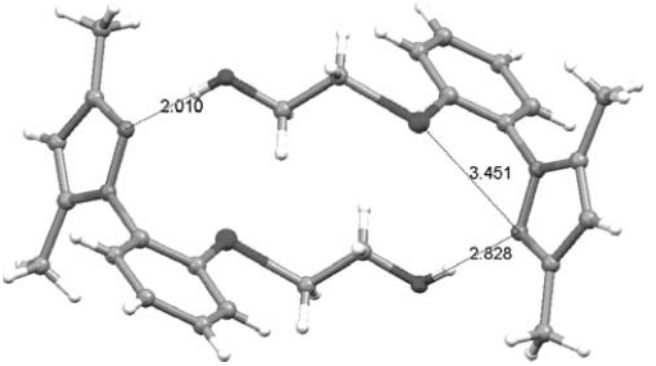
GRAPHICAL ABSTRACT



Abstract *The synthesis of a series of 2-(3,5-dimethylpyrazol-1-yl)phenyl-based organoselenium compounds, $(dmpzC_6H_4Se)_2$ (**1**), $dmpzC_6H_4SeR$ ($dmpz$ = 3,5-dimethylpyrazol-1-yl; $R = (CH_2)_nY$; Y = OH, NH_2, and COOH), and $dmpzC_6H_4SeX$ (X = Cl, Br, or I) is described. The compounds are characterized by IR, NMR (^1H, $^{13}C\{^1H\}$, $^{77}Se\{^1H\}$), and mass spectral (MS) data. The molecular structures of $(dmpzC_6H_4Se)_2$, $dmpzC_6H_4SeCH_2COOH$, and $dmpzC_6H_4SeCH_2CH_2OH$ have been established by X-ray crystallography. The two latter compounds are associated in the solid state through intermolecular hydrogen bonding between the OH proton and the pyrazolyl nitrogen atom of the adjacent molecule. Glutathione*

Received 15 February 2012; accepted 13 April 2012.

We thank Drs. T. Mukherjee, S. K. Sarkar, and D. Das for encouragement of this work. One of the authors (ASH) is grateful to Board of Research in Nuclear Sciences (BRNS), Department of Atomic Energy (DAE) for the award of a Senior Research Fellowship. We are also grateful to BRNS for the research grant under the Prospective Research Fund (PRF) Scheme (Grant no. BRNS/2007/38/5).

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peroxidase (GPx) like catalytic activity of these compounds has been evaluated by using hydrogen peroxide (H_2O_2) as substrate and dithiothreitol (DTT^{red}) as thiol cofactor in CD_3OD, and the progress of the reaction was monitored by ^1H NMR spectroscopy. All the compounds exhibited the GPx-like catalytic activity. Among these, the ones containing alkylamino groups showed the best activity.

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

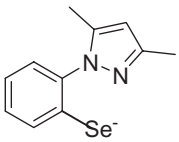
Keywords GP*x* mimicking; organoselenium compound; NMR spectroscopy; X-ray diffraction

INTRODUCTION

The chemistry of organoselenium compounds has witnessed a remarkable growth during the last two decades or so.[1,2] These compounds find numerous applications in diverse areas, like organic synthesis,[3–5] coordination chemistry,[6–8] materials science,[9,10] pharmacy,[11] antioxidants, and in many other systems.[12] In biological systems, selenium exists in the form of L-selenocysteine (Sec), an important amino acid, which constitutes an active site in selenoenzymes. The glutathione peroxidase (GP*x*) has been recognized as one of the important antioxidant selenoenzymes, which catalyzes the reduction of harmful peroxides in the presence of a thiol cofactor, viz. glutathione.[12]

Ever since the GP*x* mimicking activity of a synthetic organoselenium compound, ebselen [2-phenyl-1,2-benzoisoselenazol-3-(2*H*)-one] has been realized,[13] a myriad of low molecular weight organoselenium compounds have been designed and developed as synthetic mimics of GPx.[12] It has been observed that internally functionalized organoselenium compounds, in particular compounds containing weak Se—N interactions, show better antioxidant properties as these interactions stabilize the reaction intermediates formed during the GP*x* catalytic cycle.[14] Accordingly, different groups have synthesized several families of GP*x* active organoselenium compounds, which showed weak Se—N interactions. These include compounds containing phenyloxazoline by Singh et. al.,[15] selenenamide by Back et al.,[16] *N,N*-dialkylbenzylamines by Wilson et al.,[17] Tomoda and co-workers,[18] and Bhabak and Mugesh,[19] pyridine/quinoline by Collins et al.,[20] etc.[12d] Besides these compounds, monoselenides containing alkyl groups substituted by the OH, NH_2, and COOH groups at terminal positions also exhibit promising GP*x* mimicking activity.[21–24]

Recently, we have reported the synthesis and the GP*x* mimicking activity of 3,5-dimethylpyrazole-based organoselenium compounds.[25] These nonrigid molecules, though devoid of any intramolecular Se—N interactions, showed GP*x*-like activity. With an aim to facilitate Se—N interactions, we have now designed 2-phenyl(3,5-dimethylpyrazol-1-yl) selenides (Scheme 1) that could have such interactions and may also exhibit enhanced GP*x*-like activity. Results of this work are reported herein.

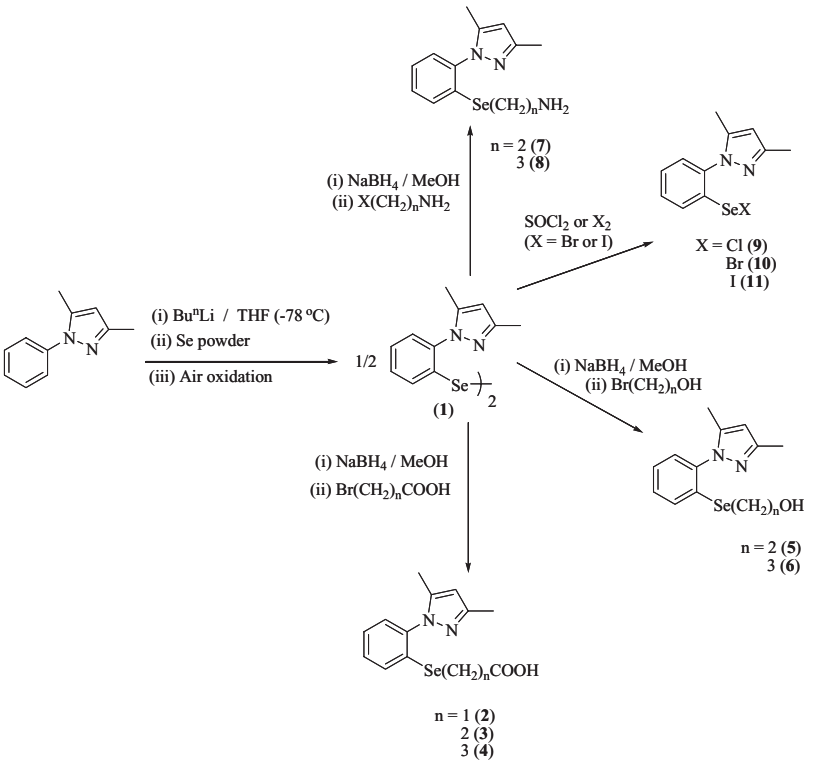


Scheme 1

RESULTS AND DISCUSSION

Synthesis and Spectroscopy

Treatment of 1-phenyl-3,5-dimethylpyrazole with *n*-BuLi in tetrahydrofuran (THF) at −78 °C gives an *ortho*-lithiated product which on reaction with selenium powder in situ, followed by oxidative work-up afforded diselenide **1** as a yellow crystalline solid with 56% yield. The reductive cleavage of the Se–Se bond by sodium borohydride in methanol (MeOH) gives a colorless solution of $NaSeC_6H_4dmpz$, which reacts with a variety of organic halo compounds to yield a series of asymmetric monoselenides, **2**–**8** (Scheme 2). Oxidation of **1** with $SOCl_2$ or X_2 (X = Br or I) in chloroform affords halo compounds $dmpzC_6H_4SeX$ [X = Cl (**9**), Br (**10**), and I (**11**)]. It is worth noting that the reaction of diorganodiselenides with iodine yields either a charge-transfer complex $(R_2Se.I_2)$[26, 27] or selenenyl iodide (RSeI),[15,28] depending on the nature of the substituent R at selenium. Selenenyl iodide has been isolated with the R groups, which are either sterically demanding[28] or capable of forming intramolecular Se—N nonbonding interactions as in $N{-}CMe_2{-}CH_2{-}O{-}C{-}C_6H_4SeI$.[15]



Scheme 2

The ^1H and $^{13}C\{^1H\}$ NMR spectra displayed the expected resonances and peak multiplicities. The methyl (δ = 2.05–2.18 and 2.26–2.32) and CH-4 (δ = 5.95–6.04) proton resonances for the dmpz group of compounds **1**–**8** appeared in a narrow region, while in the selenenyl halides **9**–**11** these resonances are considerably deshielded. Similarly in the

$^{13}C\{^1H\}$ NMR spectra of **9**–**11**, the resonances due to methyl and CH-4 carbons are significantly deshielded, while resonances for C-3 and C-5 carbons are shielded with reference to the corresponding signals for **1**–**8**. The observed deshielding of the methyl and CH-4 resonances in the ^1H and $^{13}C\{^1H\}$ NMR spectra of **9**–**11** relative to other derivatives may be attributed to a reduced electron density in the dmpz group caused by electron withdrawal by the halide ligand via Se—N interaction. The $SeCH_2$ protons in **2** appeared as a singlet in the ^1H NMR spectrum and showed ^2J(Se—H) coupling of 16.5 Hz. The $SeCH_2$ resonances for **2**–**8** showed ^1J(Se—C) couplings of 62–68 Hz. The observed magnitude of ^1J(Se—C) is in accordance with the literature values reported for organoselenium compounds with the selenium bonded to a sp^3 hybridized carbon.[29] The carbonyl carbon resonance in the $^{13}C\{^1H\}$ NMR spectra of **2**–**4** appeared in the region 172.7–176.7 and is progressively deshielded with increasing carbon chain length from one (as in **2**) to three (as in **4**). The $^{77}Se\{^1H\}$ NMR resonance in **2**–**4** is progressively shielded with increasing the chain length, for example, $\delta = 308$ (for **2**), 282 (for **3**), and 260 ppm (for **4**). The $^{77}Se\{^1H\}$ NMR resonances for monoselenides (**2**–**8**) are shielded relative to the corresponding diselenide (**1**), a trend generally encountered for organoselenium compounds.[30] The $^{77}Se\{^1H\}$ NMR resonances for selenenyl halides are considerably deshielded ($\delta = 865.6$ for **9** and 846 for **10**) with respect to diselenide **1**. The observed shifts are in accordance with RSeX chemical shifts reported in the literature.[15,31]

The mass spectra (MS) showed molecular ion peaks together with a fragment $dmpzC_6H_4Se^+$. The peaks exhibited the expected isotopic pattern. The MS of the iodo compound **11** also showed a peak attributable to the diselenide **1**. The iodides are known to equilibrate with diselenide[9] due to similar electronegativities of selenium and iodine. The compounds **9** and **10** are quite stable and did not display any peak for diselenide.

Crystal Structures of 1, 2, and 5

The ORTEP-II drawing with atomic number schemes of $(dmpzC_6H_4Se)_2$ (**1**), $dmpzC_6H_4SeCH_2COOH$ (**2**), and $dmpzC_6H_4SeCH_2CH_2OH$ (**5**) are shown in Figures 1–3, while selected interatomic parameters are given in Tables 1–3. The crystals of diselenide **1** contained four different molecules, which differ from each other by the relative orientation of the C_6H_4 and dmpz rings and slight differences in bond angles and torsion angles. The structure of **1** represents an interesting example of polymorphism in organoselenium compounds. Attempts to isolate only one form by crystallizing the compound from different solvents met with little success as the crystals of either poor quality or containing all the four molecules could be obtained. The Se—Se bond lengths (av. 2.32 Å) are well in agreement with the values reported for other diselenides which range from 2.29 to 2.39 Å.[10,32,33] The C—Se—Se—C torsion angles in all the four molecules are as expected.[32–35] The tertiary nitrogen atom of the dmpz group shows intramolecular nonbonding interaction with the selenium atom bound to the same C_6H_4dmpz unit. There are two unequal Se—N distances (~2.90 and 3.30 Å). These distances are significantly shorter than the sum of the van der Waals radii of 3.5 Å. Nonbonding Se—N interactions have been reported in organoselenium compounds, such as bis[2-(4,4-dimethyl-2-oxazolinyl)phenyl]diselenide,[15] bis[(2-dialkylaminomethyl)phenyl]diselenide,[19a,36] and bis[3,5-dimethyl-2-pyridyl]diselenide.[32]

The Se—C distances in **1**, **2**, and **5** lie in the range 1.894 (8)–1.963 (8) Å with the Se—C distances associated with $dmpzC_6H_4$ fragment being shorter than those connected

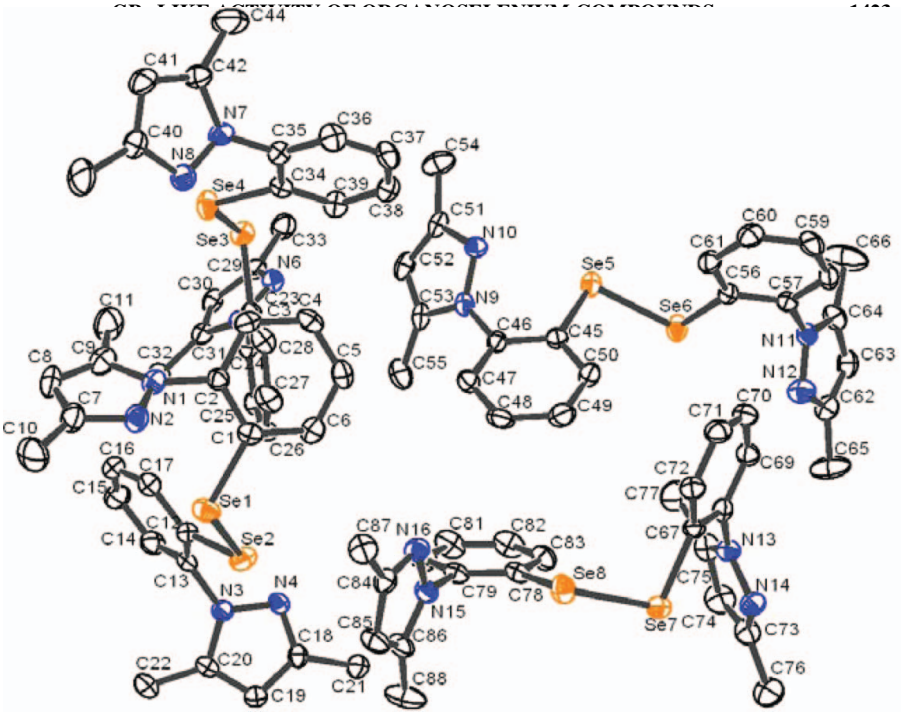


Figure 1 ORTEP-II diagram of $(dmpzC_6H_4Se)_2$ (**1**) (ellipsoids drawn with 25% probability) (Color figure available online).

with aliphatic carbon. These distances are well within the range reported for organoselenium compounds.[15,25,37,38]

The monoselenides **2** and **5** represent a ''V''-shaped configuration around the selenium atom with C—Se—C angles of 101.2(3)° (**2**) and 103.1(3)° (**5**). The observed angles are slightly opened-up as compared to the range (∼98°) reported for RSeR′ compounds, for example, $Se(CH_2COOH)_2$ (98.17(7)°,[39] $Se(CH_2CH_2COOH)_2$ (96.48(8)°,[40] $pySeCH_2COOH$ (99.67(9)°, etc.[38] Both compounds are associated through hydrogen bonding to form dimers. The hydroxyl proton makes a bond with the pyrazolyl nitrogen atom

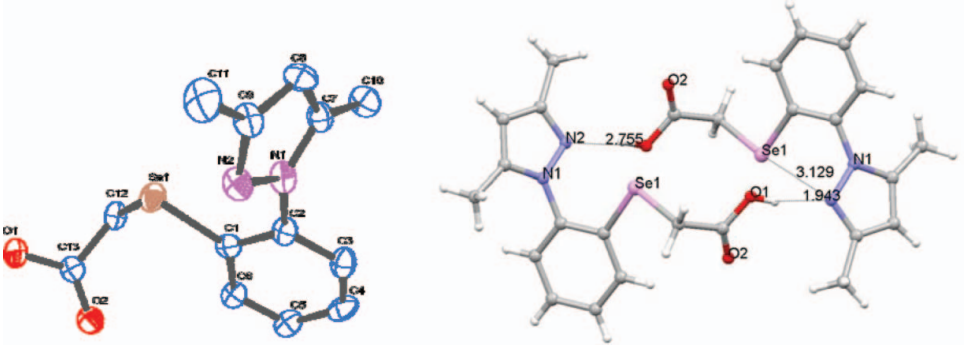


Figure 2 Molecular structure of $dmpzC_6H_4SeCH_2COOH$ (**2**) (angle between C_6H_4 and dmpz rings 60.13° and Se1–N2 = 3.129 Å) (ellipsoids drawn with 50% probability) (Color figure available online).

Table 1 Selected bond lengths (Å), bond angles (°), and torsion angles (°) for ($dmpzC_6H_4Se$)[a]

Molecule a		Molecule b		Molecule c		Molecule d	
Se(1)−Se(2)	2.3226 (15)	Se(3)−Se(4)	2.3239 (15)	Se(5)−Se(6)	2.3257 (16)	Se(7)−Se(8)	2.3212 (5)
Se(1)−C(1)	1.918 (6)	Se(3)−C(23)	1.921 (7)	Se(5)−C(45)	1.925 (7)	Se(7)−C(67)	1.923 (6)
Se(2)−C(12)	1.917 (7)	Se(4)−C(34)	1.929 (6)	Se(6)−C(56)	1.929 (6)	Se(8)−C(78)	1.933 (7)
N(1)−N(2)	1.376 (7)	N(5)−N(6)	1.371 (6)	N(9)−N(10)	1.374 (6)	N(13)−N(14)	1.366 (7)
N(3)−N(4)	1.366 (6)	N(7)−N(8)	1.367 (7)	N(11)−N(12)	1.357 (7)	N(15)−N(16)	1.374 (6)
C(1)−Se(1)−Se(2)	101.97 (19)	C(23)−Se(3)−Se(4)	100.6 (2)	C(45)−Se(5)−Se(6)	100.8 (2)	C(67)−Se(7)−Se(8)	101.95 (19)
C(12)−Se(2)−Se(1)	101.3 (2)	C(34)−Se(4)−Se(3)	101.03 (19)	C(56)−Se(6)−Se(5)	100.77 (19)	C(78)−Se(8)−Se(7)	101.2 (2)
Se(1)−C(1)−C(2)	119.3 (5)	Se(3)−C(23)−C(24)	118.4 (5)	Se(5)−C(45)−C(46)	118.7 (6)	Se(7)−C(67)−C(68)	119.2 (5)
Se(1)−C(1)−C(6)	122.2 (5)	Se(3)−C(23)−C(28)	124.2 (5)	Se(5)−C(45)−C(50)	123.5 (5)	Se(7)−C(67)−C(72)	123.4 (5)
Se(2)−C(12)−C(13)	117.4 (5)	Se(4)−C(34)−C(35)	118.2 (5)	Se(6)−C(56)−C(57)	117.2 (5)	Se(8)−C(78)−C(79)	117.5 (5)
Se(2)−C(12)−C(17)	124.5 (5)	Se(4)−C(34)−C(39)	122.4 (5)	Se(6)−C(56)−C(61)	123.9 (5)	Se(8)−C(78)−C(83)	123.7 (6)
C(2)−N(1)−N(2)	118.3 (5)	C(24)−N(5)−N(6)	118.7 (5)	C(46)−N(9)−N(10)	118.7 (5)	C(68)−N(13)−N(14)	117.9 (6)
C(13)−N(3)−N(4)	119.7 (5)	C(35)−N(7)−N(8)	119.2 (5)	C(57)−N(11)−N(12)	118.1 (5)	C(79)−N(15)−N(16)	120.2 (5)
C(1)−Se(1)−Se(2)−C(12)	−89.7 (3)	C(23)−Se(3)−Se(4)−C(34)	90.8 (3)	C(45)−Se(5)−Se(6)−C(56)	−92.4 (3)	C(67)−Se(7)−Se(8)−C(78)	90.2 (3)

[a]Angles between C_6H_4 and dmpz rings and Se N distances: 57.32° 139 (Se1 N2 = 2.920 Å), 82.81° (Se2 N4 = 3.361 Å); 51.66° (Se3 N6 = 2.891 Å), and 69.20° 140 (Se4 N8 = 3.250 Å); 57.10°(Se7 N14 = 2.906 Å), and 87.10° (Se8 N16 = 3.352 Å), 50.28° 141 (Se6 N12 = 2.874 Å), and 71.46° 142 (Se6 N12 = 3.286 Å).

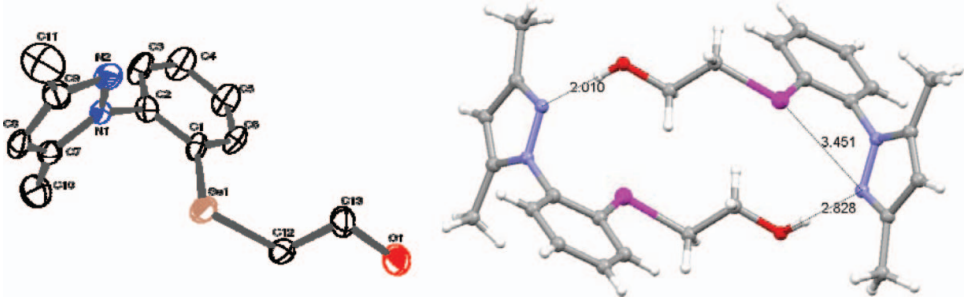


Figure 3 Molecular structure of dmpz$C_6H_4SeCH_2CH_2OH$ (**5**) (angle between C_6H_4 and dmpz rings 88.96º and Se1–N2 = 3.451 Å) (ellipsoids drawn with 50% probability) (Color figure available online).

N(2) of the adjacent molecule (1.94 Å in **2** and 2.01 Å in **5**). The organoselenium compounds containing terminal carboxylic acid groups show various degrees of association through hydrogen bonding, which vary from dimeric structures [e.g., $Se(CH_2COOH)_2$,[39] $dmpzCH_2CH_2SeCH_2CH_2COOH$[25], etc.] to infinite chains [e.g., $Se(CH_2CH_2COOH)_2$,[40] $pySeCH_2COOH$,[38] $dmpzCH_2CH_2SeCH_2COOH$[25], etc.]. Interestingly, there are weak intramolecular nonbonding Se—N interactions with the pyrazolyl nitrogen atom N(2) of 3.13 Å in **2** and 3.45 Å in **5**. Such interactions in flexible pyrazolyl derivatives $dmpzCH_2CH_2Se(CH_2)_nCOOH$ (n = 1 or 2) (Se—N = ~5 Å) are absent as the Se—N distances are much longer than the sum of their van der Waals radii of 3.5 Å.[25] The Se—N interaction in the latter molecule results in enhanced GP*x*-like activity (Figure 4).

Catalytic Properties as Mimics of GP*x*

Different methods are reported in the literature to estimate catalytic activities of organoselenium compounds as the GP*x* mimics, these include: absorption spectroscopy-based NADPH-reductase coupled assay, high-performance liquid chromatography (HPLC)-based thiol–dithiol conversion assays, and the NMR-based methods. In this study, we have evaluated the GP*x* activity by the NMR method (see Experimental section). During the course of the reaction, the resonances at δ = 2.63 and 3.67 due to dithiothreitol (DTT^{red}) decreased with concomitant increase of signals at δ = 2.87, 3.03, and 3.49 due to DTT^{ox}. Time-dependent variation in the percentage of DTT^{red} in the presence of an

Table 2 Selected bond lengths (Å) and bond angles (°) for dmpz$C_6H_4SeCH_2COOH$

Se(1)—C(1)	1.894 (8)	O(1)—H(1)	0.8200
Se(1)—C(12)	1.963 (8)	N(1)—C(2)	1.442 (10)
O(1)—C(13)	1.295 (10)	N(1)—N(2)	1.387 (8)
O(2)—C(13)	1.215 (10)		
C(1)—Se(1)—C(12)	101.2 (3)	C(12)—C(13)—O(2)	121.8 (8)
Se(1)—C(1)—C(2)	118.6 (6)	C(1)—C(2)—N(1)	119.6 (7)
Se(1)—C(1)—C(6)	124.2 (7)	C(2)—N(1)—N(2)	118.9 (7)
Se(1)—C(12)—C(13)	110.5 (5)	O(1)—C(13)—O(2)	126.2 (9)
C(12)—C(13)—O(1)	112.0 (8)		

Table 3 Selected bond lengths (Å) and bond angles (°) for dmpz$C_6H_4SeCH_2CH_2OH$

Se(1)−C(1)	1.917 (7)	N(1)−C(2)	1.428 (7)
Se(1)−C(12)	1.944 (6)	N(1)−N(2)	1.376 (7)
C(13)−O(1)	1.415 (7)		
C(1)−Se(1)−C(12)	103.1 (3)	O(1)−C(13)−C(12)	109.5 (6)
Se(1)−C(12)−C(13)	113.2 (5)	N(2)−N(1)−C(2)	119.0 (7)
Se(1)−C(1)−C(2)	116.3 (6)	C(1)−C(2)−N(1)	120.1 (7)
Se(1)−C(2)−C(6)	125.4 (6)		

organoselenium compound is shown in Figure 5. The t_{50} value is used as a measure to estimate the GP*x* catalytic efficacy of compounds. At a concentration of 1.6 μmol, the t_{50} for dmpz$C_6H_4SeCH_2CH_2NH_2$ (**7**) was 5 min, while that for dmpz$C_6H_4SeCH_2CH_2CH_2NH_2$ (**8**) at the same concentration was <3 min. The t_{50} values estimated from these plots for various organoselenium compounds are summarized in Table 4, and their relative activities are in the order of **8** > **7** > **9** > **10** > **1** > **11** > **5** > **6** > **3** > **4** > **2**. From these results, it is evident that **8** is the most active organoselenium compound in reducing hydrogen peroxide (H_2O_2). The higher activity for **7** and **8** in MeOH could be due to the presence of an amino group, which acts as either a base catalyst for the GP*x* reaction or the functional group that increases the electron density at selenium atom.

The redox reaction is proposed to proceed through the intermediacy of selenoxide formation.[41] To detect any possible formation of selenoxide intermediates of the tested organoselenium compounds, the reactions were followed by the $^{77}Se\{^1H\}$ NMR

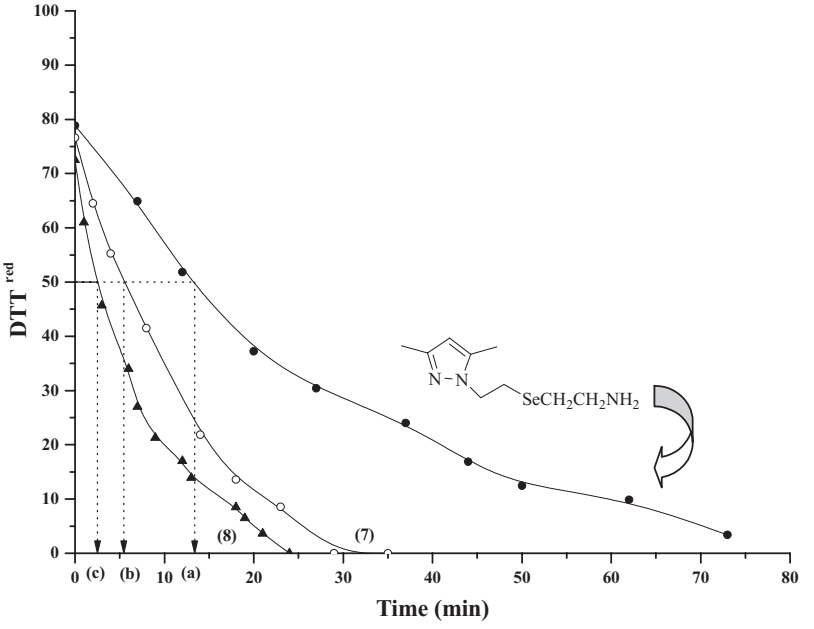


Figure 4 DTT^{red} = 23.1 mg (0.15 mmol), H_2O_2 = 9.5 μL (45.96%, 0.15 mmol), catalyst concentration = 1.6 μmol.

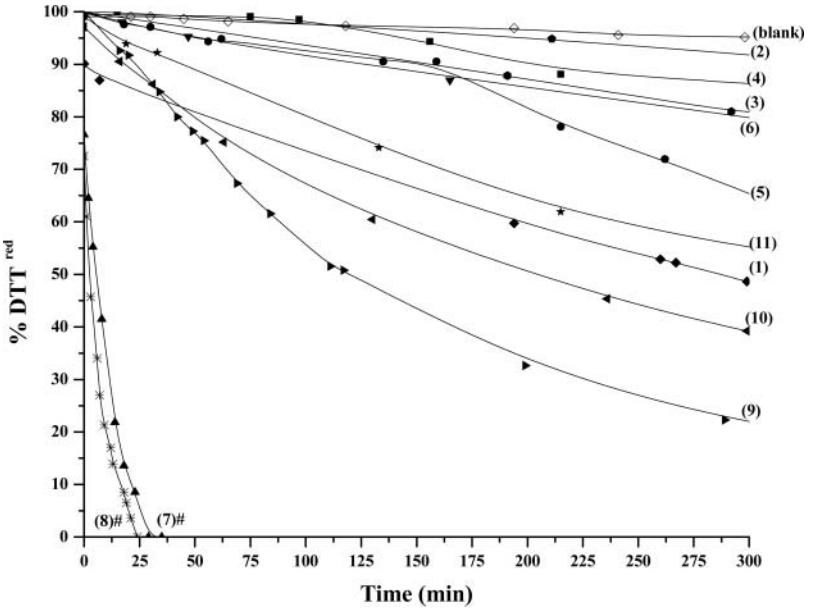


Figure 5 Percentages of residual DTT^{red} as a function of the reaction time in the oxidation of DTT^{red} with H_2O_2 in the presence of organoselenium catalysts in CD_3OD. Reaction conditions: $[DTT^{red}]_0 = [H_2O_2]_0 = 0.15$ mM and [selenide] = 7.5 μmol; **7** and **8** it is 1.6 μmol, at 25 °C.

spectroscopy. The chemical shift values for some selected selenoxide analogues of 2-(3,5-dimethylpyrazol-1-yl)phenylseleno compounds are given in Table 5. For instance, the $^{77}Se\{^1H\}$ NMR resonance for $dmpzC_6H_4SeCH_2CH_2CH_2OH$ ($\delta = 261.7$) is highly deshielded on treatment with 1 mol equivalent of H_2O_2, indicating the formation of the corresponding selenoxide, $dmpzC_6H_4Se(O)CH_2CH_2CH_2OH$ ($\delta = 858$).

Table 4 The t_{50} values of organoselenium compounds (concentration 7.5 μmol) estimated by ^1H NMR spectroscopy

Compound		t_{50} in min
Blank		>300
$(dmpzC_6H_4Se)_2$	(**1**)	285
$dmpzC_6H_4SeCH_2COOH$	(**2**)	>300
$dmpzC_6H_4SeCH_2CH_2COOH$	(**3**)	>300
$dmpzC_6H_4SeCH_2CH_2CH_2COOH$	(**4**)	>300
$dmpzC_6H_4SeCH_2CH_2OH$	(**5**)	>300
$dmpzC_6H_4SeCH_2CH_2CH_2OH$	(**6**)	>300
$dmpzC_6H_4SeCH_2CH_2NH_2$	(**7**)	5[a]
$dmpzC_6H_4SeCH_2CH_2CH_2NH_2$	(**8**)	<3[a]
$dmpzC_6H_4SeCl$	(**9**)	119
$dmpzC_6H_4SeBr$	(**10**)	202
$dmpzC_6H_4SeI$	(**11**)	>300

[a]Concentration of selenium compound 1.6 μmol.

Table 5 $^{77}Se\{^{1}H\}$ NMR spectral data for 2-(3,5-dimethylpyrazole-1-y)lphenylselenoxides in $CDCl_3$

Compound	$^{77}Se\{^{1}H\}$ NMR (δ in ppm)
$dmpzC_6H_4Se(O)CH_2COOH$	1215
$dmpzC_6H_4Se(O)CH_2CH_2COOH$	1253
$dmpzC_6H_4Se(O)CH_2CH_2CH_2COOH$	1258
$dmpzC_6H_4Se(O)CH_2CH_2OH$	860
$dmpzC_6H_4Se(O)CH_2CH_2CH_2OH$	858
$dmpzC_6H_4Se(O)CH_2CH_2NH_2$	857
$dmpzC_6H_4Se(O)CH_2CH_2CH_2NH_2$	860

CONCLUSIONS

A series of 2-(3,5-dimethylpyrazol-1-yl)phenyl-based organoselenium compounds have been synthesized and characterized by the NMR spectroscopy and MS. Structures of $(dmpzC_6H_4Se)_2$, $dmpzC_6H_4SeCH_2COOH$, and $dmpzC_6H_4SeCH_2CH_2OH$, revealed the presence of intermolecular Se−N interactions. The two latter compounds are associated through hydrogen bonding leading to the formation of dimers. The unsymmetrical monoselenides containing alkyl chains substituted by amino group at terminal position showed the best GP*x* like activity.

EXPERIMENTAL

Materials and Methods

Elemental selenium (99.99%), sodium borohydride, *n*-butyllithium (1.6 M hexane solution), bromoacetic acid, 3-bromopropionic acid, 4-bromobutyric acid, 2-bromoethylamine hydrobromide, 3-chloropropylamine hydrochloride, 2-bromoethanol, and 3-bromopropanol were purchased from commercial sources (Aldrich/Fluka). All reactions were carried out under a nitrogen atmosphere. Solvents were purified and dried by standard procedures[42] and were distilled prior to use. The purity of 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 Thermo Fischer EA 1112 CHNS Analyzer. IR spectra (ν, cm^{-1}) were recorded on a JASCO FT IR-6100 spectrometer. The 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 ($^{77}Se\{^{1}H\}$). The ^{1}H and $^{13}C\{^{1}H\}$ NMR chemical shifts were relative to internal chloroform peak ($\delta = 7.26$ for ^{1}H and $\delta = 77.0$ for $^{13}C\{^{1}H\}$ NMR). The $^{77}Se\{^{1}H\}$ NMR chemical shifts were relative to external diphenyl diselenide (Ph_2Se_2) in $CDCl_3$ (δ 463.0 relative to Me_2Se ($\delta = 0$). The MS were recorded on a MS-500 Ion Trap (IT) Varian mass spectrometer at Sophisticated Analytical Instrumentation Facility (SAIF), Indian Institute of Technology Bombay, Mumbai.

Synthesis

Bis[2-(3,5-dimethylpyrozol-1-yl)phenyl]diselenide, $(dmpzC_6H_4Se)_2$ (1). To a cold (−78 °C) solution (250 mL) of 3,5-dimethyl-1-phenylpyrazole (15 g, 81.5 mmol) in dry THF, *n*-BuLi (80 mL, 1.6 M hexane solution) was added dropwise with stirring

under a N_2 atmosphere. The reaction mixture was brought to room temperature and stirred for additional 1 h. The reactants were again cooled to −78 °C. To this, Se (9.1 g, 115 mmol) powder was added and the temperature was maintained for 1 h with constant stirring. The reaction mixture was allowed to stir for 4 h at room temperature and finally it was acidified with excess of aq. NH_4Cl. The reaction mixture was left in an open atmosphere overnight and extracted with diethyl ether (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to yield a dark orange sticky solid. The residue was purified by column chromatography using hexane–ethyl acetate mixture (70:30) as an eluent to afford a yellow crystalline solid (12.0 g, 56%), mp: 125–128 °C. ^{1}H NMR ($CDCl_3$): 2.18, 2.31 (each s, 3H, CH_3), 6.02 (s, 1H, dmpz-*H*), 7.17–7.20 (m, 1H, ArH), 7.22–7.28 (m, 2H, ArH), 7.75–7.78 (m, 1H, ArH). ^{13}C{^{1}H} NMR ($CDCl_3$): 11.6, 13.4 (each s, CH_3), 106.4 (dmpz-4*C*), 126.0, 127.0, 129.1, 130.4, 131.4, 137.9 (C_6H_4), 139.8, 148.8 (dmpz-3*C*, 5*C*). ^{77}Se{^{1}H} NMR ($CDCl_3$): 417.0. MS: *m*/*z*: 524.9 [$(M+Na)^+$, 100], 501.1(M^+, 99.8), 251 (SeC_6H_4dmpz, 86.45). Anal. calcd. for $C_{22}H_{22}N_4Se_2$: C, 52.81; H, 4.43; N, 11.20. Found: C, 52.55; H, 4.32; N, 10.81.

2-(3,5-Dimethylpyrozol-1-yl)phenylselenoethanoic acid, dmpz$C_6H_4SeCH_2COOH$ (2). To a methanolic (25 mL) yellow solution of **1** (1.1 g, 2.2 mmol), solid $NaBH_4$ (167 mg, 4.4 mmol) was added in small portions with vigorous stirring under a N_2 atmosphere whereupon a colorless solution was formed. To this, a methanolic solution of bromoacetic acid (612 mg, 4.4 mmol) was added and the reaction mixture was then stirred for 4 h. MeOH was evaporated in vacuo and the residue was extracted with ethyl acetate. It was dried over Na_2SO_4 and the solvent was evaporated in vacuo to give a colorless crystalline solid (1.1 g, 80%). Mp: 117–120 °C. IR: 2870 (COOH), 1705 (CO). ^{1}H NMR ($CDCl_3$): 2.11, 2.32 (each s, 3H, CH_3), 3.32 (s, $^2J_{Se-H}$ = 16.5 Hz, 2H, CH_2COOH), 6.04 (br, 2H, dmpz-*H* and COOH), 7.24–7.27 (m, 1H, ArH), 7.33–7.42 (m, 2H, ArH), 7.72–7.75 (m, 1H, C_6H_4). ^{13}C{^{1}H} NMR ($CDCl_3$): 11.4, 13.0 (each s, CH_3), 26.5 (J_{C-Se} = 68 Hz, $SeCH_2$), 106.0 (dmpz-4*C*), 127.9, 128.2, 130.2, 130.5, 133.1, 138.9 (C_6H_4), 141.1, 148.9 (dmpz-3*C*, 5*C*), 172.7 (COOH). ^{77}Se{^{1}H} NMR ($CDCl_3$): 308.0. MS: *m*/*z*: 309.0 [$(MH)^+$, 43.5], 251 (SeC_6H_4dmpz, 12.96). Anal. calcd. for $C_{13}H_{14}N_2O_2Se$: C, 50.49; H, 4.56; N, 9.06. Found: C, 49.93; H, 4.46; N, 8.73.

The compounds **3**–**8** were prepared in the same way as described for **2** using corresponding bromo derivatives instead of bromoacetic acid. Characterization data are given in the Supplementary Materials (available online).

2-(3,5-Dimethylpyrozol-1-yl)phenylselenyl chloride, dmpzC_6H_4SeCl (9). To solid **1** (200 mg, 0.4 mmol) in a 25 mL round bottom (RB) flask, $SOCl_2$ (5 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 4 h under reflux. The solvent was evaporated in vacuo to give an off white solid which was then re-crystallized from a dichloromethane (DCM)−MeOH mixture affording a pale yellow crystalline product (195 mg, 85%), mp: 175 °C (decomp.). ^{1}H NMR ($CDCl_3$): 2.38, 2.73 (each s, 3H, CH_3), 6.17 (s, 1H, dmpz-*H*), 7.32–7.39 (m, 2H, C_6H_4), 7.63–7.66 (m, 1H, ArH), 8.46–8.49 (m, 1H, C_6H_4). ^{13}C{^{1}H} NMR ($CDCl_3$): 12.8, 14.3 (each s, CH_3), 110.7 (dmpz-4*C*), 114.6, 126.6, 130.0, 134.3 (C_6H_4), 137.7, 143.5 (dmpz-3,5-*C*). ^{77}Se{^{1}H} NMR ($CDCl_3$): 865.6. MS: *m*/*z*: 309 [$(M+H+Na)^+$, 100], 307 [$(MNa-H)^+$, 54.48], 251 (SeC_6H_4dmpz, 25.64). Anal. calcd. for $C_{11}H_{11}ClN_2Se$: C, 46.25; H, 3.88; N, 9.81. Found: C, 45.83; H, 3.65; N, 9.53.

2-(3,5-Dimethylpyrozol-1-yl)phenylselenyl bromide, dmpzC_6H_4SeBr (10). To a chloroform solution (25 mL) of **1** (200 mg, 0.4 mmol) a solution of bromine (0.02 mL, 0.0639 g, 0.4 mmol) in chloroform was added dropwise at 0 °C over a period

of 15 min. The reaction mixture was allowed to stir for 30 min. whereupon a yellow precipitate formed. The chloroform was then evaporated in vacuo to afford a yellow crystalline solid (205 mg, 78%), mp: 200 °C (decomp.). ^{1}H NMR ($CDCl_3$): 2.38, 2.71 (each s, 3H, CH_3), 6.16 (s, 1H, dmpz-*H*), 7.30–7.40 (m, 2H, C_6H_4), 7.58–7.61 (d, J = 7.8 Hz, 1H, C_6H_4), 8.48–8.50 (d, J = 7.5 Hz, 1H, ArH). ^{13}C{^{1}H} NMR ($CDCl_3$): 12.8, 14.3 (each s, CH_3), 110.7 (dmpz-4*C*), 114.9, 126.7, 131.8, 134.5 (C_6H_4), 137.8, 143.6 (dmpz-3,5-*C*). ^{77}Se{^{1}H} NMR ($CDCl_3$): 846.0. Mass: *m*/*z*: 331 [$(M+H)^+$, 11.5], 251 (SeC_6H_4dmpz, 100). Anal. calcd. for $C_{11}H_{11}BrN_2Se$: C, 40.03; H, 3.36; N, 8.49. Found: C, 40.22; H, 3.29; N, 8.01. Similarly compound **11** was prepared (Supplementary Material available online).

X-Ray Crystallography. Single crystal X-ray diffraction data for (dmpz$C_6H_4Se)_2$ (**1**), dmpz$C_6H_4SeCH_2COOH$ (**2**), and dmpz$C_6H_4SeCH_2CH_2OH$ (**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 $\theta_{max} = 27.5°$. The unit cell parameters (Table 6) were determined from 25 reflections measured by a random search routine. The intensity data were corrected for Lorentz, polarization, and absorption effects with an empirical procedure.[43] The structures were solved by direct methods using SHELX-97[44] and refined by full-matrix least squares methods. The nonhydrogen atoms were refined anisotropically. The hydrogen atoms were fixed in their calculated positions. The molecular structures were drawn by ORTEP-II.[45]

GP*x* Activities

The GP*x* like activity of these compounds was monitored by the ^{1}H NMR spectroscopy.[24,41] In this method, the reaction between H_2O_2 and DTT^{red} (reduced dithiothreitol) was monitored both in the presence and absence of a selenium catalyst. In a typical experiment, DTT^{red} (0.15 mmol) and organoselenium compound (7.5 μmol) were dissolved in CD_3OD (0.5 mL) and the reaction was initiated by addition of freshly standardized H_2O_2 (47.6%) (0.15 mmol). This point was considered as zero time. Progress of the reaction was monitored by ^{1}H NMR spectroscopy over a period of 0–300 min. The relative concentration of DTT^{red} (δ = 3.67 for CH protons) and DTT^{ox} (δ = 3.49 for CH protons) was estimated by integrating their respective resonances. The time required (t_{50}) 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 thiol cofactor (DTT^{red}). For control, similar experiment was performed in the absence of organoselenium compound.

SUPPLEMENTAL DATA

Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre, CCDC nos. 835733 [(dmpz$C_6H_4Se)_2$], 835732 (dmpz$C_6H_4SeCH_2COOH$), and 835731 (dmpz$C_6H_4SeCH_2CH_2OH$). Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223-336-033; E-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk].

†**Supplemental Materials** (see footnote on the first page of this article): Some experimental details and characterization data of organoselenium compounds, as well as the cif files of the single crystal X-ray diffraction analyses of compounds **1**, **2**, and **5** are available.

Table 6 Crystallographic and structural refinement data for $(dmpzC_6H_4Se)_2$, $dmpzC_6H_4SeCH_2COOH$, and $dmpzC_6H_4SeCH_2CH_2OH$

Compound	$(dmpzC_6H_4Se)_2$	$dmpzC_6H_4SeCH_2COOH$	$dmpzC_6H_4SeCH_2CH_2OH$
Chemical formula	$C_{22}H_{22}N_4Se_2$	$C_{13}H_{14}N_2O_2Se$	$C_{13}H_{16}N_2OSe$
Formula weight	500.36	309.22	295.24
Color of crystal	Yellow	Colorless	Colorless
Crystal size	0.40 × 0.40 × 0.10	0.30 × 0.30 × 0.30	0.25 × 0.20 × 0.16
Crystal system/space group	Triclinic, $P\bar{1}$	Monoclinic, $P2_1/c$	Monoclinic, $C2/c$
a (Å)	11.413 (7)	8.443 (3)	24.000 (8)
b (Å)	14.750 (7)	13.376 (6)	8.097 (4)
c (Å)	26.584 (11)	12.064 (6)	15.169 (6)
α (°)	98.11 (4)	90.00	90.00
β (°)	95.06 (4)	99.57 (4)	111.37 (3)
γ (°)	90.12 (5)	90.00	90.00
V (Å^3)	4413 (4)	1343.5 (10)	2745.0 (19)
Z	8	4	8
D_c (g/cm^3)	1.506	1.529	1.429
μ(Mo Kα) mm^{-1}/F (000)	3.366/2000	2.791/624	2.722/1200
Limiting indices	$-8 \le h \le 14$	$-10 \le h \le 6$	$-17 \le h \le 30$
	$-19 \le K \le 19$	$-17 \le k \le 0$	$-10 \le k \le 5$
	$-34 \le l \le 34$	$-15 \le l \le 15$	$-19 \le l \le 18$
θ Range for data collection	2.53–27.50	2.88–27.55	2.68–27.52
No. of reflections collected	24,384	3031	4200
No. of independent reflections	20,217	1048	3125
Data/restraints/parameters	20,217/0/1025	3031/0/167	3125/0/158
R indices [$I > 2\sigma$ (I)]	$R_1 = 0.0500$; $WR_2 = 0.0874$	$R_1 = 0.0704$; $WR_2 = 0.1686$	$R_1 = 0.0637$; $WR_2 = 0.0818$
R indices (all data):	$R_1 = 0.2389$; $WR_2 = 0.1279$	$R_1 = 0.2434$; $WR_2 = 0.2417$	$R_1 = 0.3065$; $WR_2 = 0.1209$
$(\Delta/\sigma)_{max}$	0.037	0.000	0.000
$(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$ (Å^{-3})	0.435, −0.488	0.721, −1.203	0.370, −0.441
Goodness of fit (gof) on F^2	0.930	0.916	0.885

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