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합성, 2,4-Diaryl-1,3-selenazoles의 항바이러스 활성도와 반응

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요 약. α-Bromoketones을 가진 1차 arylselenocarboxylic amide의 고리화는 여러가지 새로운 2,4-diaryl-1,3-selenazoles에 사용되었다. 염소, 브롬, 요오드를 사용한 2,4-diaryl-1,3-selenazoles의 할로겐화는 좋은 수율의 새로운 1,1-dihalo-2,4-diaryl-1,3-selenazoles를 준다. AIDS virus(HIV-1 and HIV-2)에 대하여 몇몇의 1,1-dihalo-2,4-diaryl-1,3-selenazoles의 항바이러스 활성도를 검사하였다. 그것들은 HIV-1에 대한 약간의 대생물활성을 보였다. 모든 화합물은 원소분석, ^{1}H NMR 그리고 질량 분광분석 정보로 구조분석 하였다. 2-(3,4-dimethoxyphenyl)-4-(4-bromophenyl)-1,3-selenazole의 결정구조도 보였다.

주제어: 1,3-Selenazoles, arylselenocarboxamides, α-bromoketones, X-ray, HIV-1

ABSTRACT. The cyclization of primary arylselenocarboxylic amides with α-bromoketones afforded a variety of new 2,4-diaryl-1,3-selenazoles. Halogenation of the 2,4-diaryl-1,3-selenazoles with chlorine, bromine and iodine gave the new 1,1-dihalo-2,4-diaryl-1,3-selenazoles in good yields. Antiviral activity of some 1,1-dihalo-2,4-diaryl-1,3-selenazoles has been tested against AIDS virus (HIV-1 and HIV-2). They showed some bioactivity against HIV-1. All compounds were characterized by their elemental analysis, ^{1}H NMR and mass spectroscopic data. The crystal structure of 2-(3,4-dimethoxyphenyl)-4-(4-bromophenyl)-1,3-selenazole displays the molecular configuration.

Keywords: 1,3-Selenazoles, arylselenocarboxamides, α-bromoketones, X-ray, HIV-1

INTRODUCTION

The synthesis of sulfur- and nitrogen containing heterocyclic compounds have been extensively studied, while the syntheses of selenium analogues have not been appreciably investigated.[1,2] This is mainly due to the difficultly in preparing primary selenocarboxamides.[3] Such compounds can be used to prepare the selenium-nitrogen heterocyclic compounds.[3b,4] The reactions of primary selenoamides

with α-haloketones have been already reported to prepare selenium-nitrogen heterocyclic compounds.[5]

Recently, however, reports of selenium-containing heterocyclic compound synthesis have gradually increased because of their interesting reactivities and their pharmaceutical applications. The selenazole derivatives are of marked interest because of their anti-tumor, antibacterial and other notable activities.[6-9] For example, selenazofurin (2-β-D-ribofuranosylselenazole-4-carboxamide) showed significant anti-tumor properties in animals and broad spectrum antiviral activity in cell culture experiments.[9] Thus, many synthetic routes of selenazole derivatives have been extensively investigated.[10]

Recently, we used arylselenocarboxamides to prepare several new 3,5-diaryl-1,2,4-selenadiazoles using palladium(II) salt as a catalyst.[4a] The present work describes the reaction of arylselenocarboxamides with α-bromoketones to prepare a variety of several unreported 2,4-diary-1,3-selenazoles. Furthermore, reactions of 2,4-diaryl-1,3-selenazoles with SO_2Cl_2, Br_2 and I_2 are reported and the biological significance of some of them was tested. The crystal structure of 2-(3,4-dimethoxyphenyl)-4-(4-bromophenyl)-1,3-selenazole has been determined by X-ray crystallography.

It is worth noting that Giesel *et al*[11] showed that the reaction of nitriles with P_2Se_5 afforded primary selenocarboxylic amides. The cyclization of these compounds with α-haloketones afforded a variety of functionalized 1,3-selenazoles.[11]

EXPERIMENTAL

Physical measurements

^{1}H and ^{13}C NMR spectra were obtained with a Jeol-EX-90FT, a Bruker LA-250(250 MHz) and a Bruker 300 spectrometer instruments. They were recorded in DMSO-d_6 or $CDCl_3$ solutions containing TMS as internal standard. Chemical shifts for all ^{1}H and ^{13}C NMR spectra were reported in δ units downfield from internal reference Me_4Si. Elemental analyses (C, H and N) were performed by Analytical Laboratories of Konstanz University, Germany. Mass spectra (EI) were determined on a Finnigan MAT-321 spectrometer at 70 eV and measurements were carried out on ^{80}Se isotope.

The structure of 2-(3,4-dimethoxyphenyl)-4-(4-bromophenyl)-1,3-selenazole(**13**) was determined by single crystal X-ray diffraction. A colourless single crystal of **13** with dimensions 0.30×0.15×0.04 mm was mounted on a thin glass fiber. Data were collected on an Enraf Nonius CAD4 automated 40 circles diffractometer (Mo Kα radiation, λ= 0.71069Å) at 293 K in the range of $2.11<\theta<22.10°$. Data were corrected for Lorentz and polarization effects. The structure was solved by direct method using SHELXS-97[12] and subsequent difference Fourier syntheses and then refined by full-matrix least-squares method on F^2 using SHELXL97.[12] All of the non-hydrogen atoms were refined anisotropically. Positions of the hydrogen atoms were fixed at their ideal positions. Refinement of $\mathbf{F^2}$ against all reflections. The weighted R-factor wR and goodness of fit S are based on $\mathbf{F^2}$, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\text{sigma}(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on all data will be even larger.

Synthesis

All reactions were carried out under dry nitrogen atmosphere. All solvents were dried and freshly distilled under nitrogen before use.

Phenylselenocarboxamide,4-bromophenylselenocarboxamide, 2-methoxyphenylselenocarboxamide, 4-methoxyphenylselenocarboxamide, 4-methylthiophenylselenocarboxamide, 4-ethoxyphenylselenocarboxamide, 2,3-dimethoxyphenylselenocarboxamide, 3,4-dimethoxyphenylselenocarboxamide, 3,5-dimethoxyphenylselenocarboxamide, 4-phenylphenylselenocarboxamide, 6-methoxynaphthyl-1-selenocarboxamide and 4-methoxynaphthyl-2-selenocarboxamide were prepared according to a literature method.[4a]

2,4-Diary-1,3-selenazoles were prepared from the reaction of the corresponding arylselenocarboxamides with α-bromoketones (phenacyl bromide, 4-

bromophenacyl bromide and 4-phenylphenyacyl bromide) by the following general procedure:

A solution of α-bromoketones (10 mmol) in 10 cm^3 of ethanol was added dropwise to a hot solution of arylselenocarboxamides (10 mmol) in 20 cm^3 ethanol. The reaction mixture was refluxed for 45-60 min (the end of the reaction was monitored by TLC). The mixture is then concentrated by a rotary evaporator and the residue neutralized with dilute aqueous ammonia (10%). The precipitate is deposited, collected by filtration and then washed several times with cold ethanol. Recrystallization from ethanol to give the corresponding 2,4-diary-1,3-selenazoles in fair to good yields.

2-Phenyl-4-(4-phenylphenyl)-1,3-selenazole (1)

Yield: 72%. M.p. 155-157 °C. Anal. Calc. for $C_{21}H_{15}NSe$: C, 70.00; H, 4.19; N, 3.88. Found: C, 69.62; H, 3.97; N, 3.86%. ^{1}H NMR(DMSO-d_6): δ 7.55-7.21(m, 6H, Ar-*H*), 7.81 (d, 4H, Ar-*H*, *J*=7.85 Hz), 8.38-7.92 (m, 4H, Ar-*H*), 8.75 (s, 1H, Ar-*H*).

MS: m/z: 361(M^+).

2,4-bis(4-Bromophenyl)-1,3-selenazole (2)

Yield: 63%. M.p. 161-163 °C. Anal. Calc. for $C_{15}H_9Br_2NSe$: C, 40.76; H, 2.05; N, 3.17. Found: C, 40.64; H, 1.98; N, 3.16%. ^{1}H NMR (DMSO-d_6): δ 7.85-7.48(m, 4H, Ar-*H*), 8.10-7.90 (m, 4H, Ar-*H*), 8.82 (s, 1H, Ar-*H*).

2-(4-Bromophenyl)-4-(4-phenylphenyl)-1,3-selenazole (3)

Yield: 77%. M.p. 188-190 °C. Anal. Calc. for $C_{21}H_{14}BrNSe$: C, 57.43; H, 3.21; N, 3.19. Found: C, 57.64; H, 3.18; N, 3.16%. ^{1}H NMR (DMSO-d_6): δ 7.52(d, 2H, Ar-*H, J*=8.25 Hz), 7.95-7.72(m, 7H, Ar-*H*), 8.28-7.96 (m, 4H, Ar-*H*), 8.80 (s, 1H, Ar-*H*).

2-(4-Hydroxyphenyl)-4-(4-bromophenyl)-1,3-selenazole (4)

Yield: 52%. M.p. 167-168 °C. Anal. Calc. for $C_{15}H_{10}BrNOSe$: C, 47.52; H, 2.66; N, 3.69. Found: C, 47.33; H, 2.53; N, 3.60%. ^{1}H NMR (DMSO-d_6): δ 6.87(d, 2H, Ar-*H, J*=8.04 Hz), 7.64(d, 2H, Ar-*H, J*=6.89 Hz), 8.20-7.74 (m, 4H, Ar-*H*), 8.60 (s, 1H, Ar-*H*), 10.09 (s, 1H, *OH*).

MS: m/z: 379/381(M^+).

2-(4-Methoxyphenyl)-4-(4-bromophenyl)-1,3-selenazole (5)

Yield: 61%. M.p. 174-176 °C. Anal. Calc. for $C_{16}H_{12}BrNOSe$: C, 48.88; H, 3.08; N. Found: C, 48.63; H, 2.93; N, 3.62%. ^{1}H NMR (DMSO-d_6): δ 3.85(s, 3H, CH_3), 7.07(d, 2H, Ar-*H*, *J*=7.25 Hz), 7.72 (d, 2H, Ar-*H*, *J*=8.22 Hz), 8.10-7.87 (m, 4H, Ar-*H*), 8.65 (s, 1H, Ar-*H*).

2-(4-Methoxyphenyl)-4-(4-phenylphenyl)-1,3-selenazole (6)

Yield: 30%. M.p. 187-188 °C. Anal. Calc. for $C_{22}H_{17}NOSe$: C, 67.69; H, 4.39; N, 3.59. Found: C, 67.63; H, 4.33; N, 3.60%. ^{1}H NMR (DMSO-d_6): δ 3.85 (s, 3H, OCH_3), 7.70-7.26 (m, 7H, Ar-*H*), 8.20-7.92 (m, 4H, Ar-*H*), 8.65 (s, 1H, Ar-*H*).

2-(2-Methoxyphenyl)-4-(4-bromophenyl)-1,3-selenazole (7)

Yield: 69%. M.p. 165-167 °C. Anal. Calc. for $C_{16}H_{12}BrNOSe$: C, 48.88; H, 3.08; N, 3.56. Found: C, 48.54; H, 2.60; N, 3.34%. ^{1}H NMR (DMSO-d_6): δ 4.10 (s, 3H, CH_3), 7.50-7.30 (m, 3H, Ar-*H*),7.68 (d, 2H, Ar-*H, J*=7.68 Hz), 8.10 (d, 2H, Ar-*H*, *J*= 8.24 Hz), 8.47 (d, 1H, Ar-*H*, *J*=8.21 Hz), 8.79 (s, 1H, Ar-*H*).

2-(2-Methoxyphenyl)-4-(4-phenylphenyl)-1,3-selenazole (8)

Yield: 55%. M.p. 175-177 °C. Anal. Calc. for $C_{22}H_{17}NOSe$: C, 67.69; H, 4.39; N, 3.59. Found: C, 67.64; H, 4.35; N, 3.54%. ^{1}H NMR (DMSO-d_6): δ 4.10 (s, 3H, CH_3), 7.68-7.00 (m, 6H, Ar-*H*),7.78 (d, 4H, Ar-*H*, *J*=7.35 Hz), 8.20 (d, 2H, Ar-*H, J*=8.04 Hz), 8.30 (d, 1H, Ar-*H*, *J*=7.45 Hz), 8.75 (s, 1H, Ar-*H*).

2-(2-Ethoxyphenyl)-4-(4-bromophenyl)-1,3-selenazole (9)

Yield: 60%. M.p. 158-160 °C. Anal. Calc. for $C_{17}H_{14}BrNOSe$: C, 50.14; H, 3.46; N, 3.44. Found: C, 49.46; H, 3.45; N, 3.32%. ^{1}H NMR (DMSO-d_6): δ 1.38(t, 3H, CH_3), 4.11 (q, 2H, CH_2), 7.04 (d, 2H, Ar-*H*, *J*= 8.05 Hz),7.63 (d, 2H, Ar-*H, J*= 8.12 Hz), 7.97 (t, 4H, Ar-*H*), 8.65 (s, 1H, Ar-*H*).

2-(2,3-Dimethoxyphenyl)-4-(4-bromophenyl)-1,3-selenazole (10)

Yield: 48%. M.p. 136-138 °C. Anal. Calc. for $C_{17}H_{14}BrNO_2Se$: C, 48.25; H, 3.33; N, 3.31. Found: C, 48.34; H, 3.45; N, 3.32%.

2-(2,3-Dimethoxyphenyl)-4-(4-phenylphenyl)-1,3-selenazole (11)

Yield: 73%. M.p. 155-157 °C. Anal. Calc. for $C_{23}H_{19}NO_2Se$: C, 65.72; H, 5.46; N, 3.30. Found: C, 65.50; H, 5.51; N, 3.28%.

MS: m/z: 421(M^+).

2-(3,5-Dimethoxyphenyl)-4-(4-bromophenyl)-1,3-selenazole (12)

Yield: 43%. M.p. 98-100 °C. Anal. Calc. for $C_{17}H_{14}BrNO_2Se$: C, 48.25; H, 3.33; Br, N, 3.44. Found: C, 48.14; H, 3.31; N, 3.29%. ^{1}H NMR (DMSO-d_6): δ 3.85(s, 6H, *OCH_3*), 6.70 (s, 1H, Ar-*H*), 7.15 (s, 2H, Ar-*H*), 7.70 (d, 2H, Ar-*H*, *J*= 8.22 Hz), 8.08 (d, 2H, Ar-*H*, *J*=7.96 Hz), 8.65 (s, 1H Ar-*H*).

2-(3,4-Dimethoxyphenyl)-4-(4-bromophenyl)-1,3-selenazole (13)

Yield: 66%. M.p. 181-182 °C. Anal. Calc. for $C_{17}H_{14}BrNO_2Se$: C, 48.25; H, 3.33; Br, N, 3.44. Found: C, 48.34; H, 3.41; N, 3.31%. ^{1}H NMR (DMSO-d_6): δ 3.90(s, 6H, *OCH_3*), 7.13 (d 1H, Ar-*H*, *J*=8.20 Hz), 7.71 (d, 4H, Ar-*H*, *J*=7.22 Hz), 8.11 (d, 2H, Ar-*H*, *J*=7.80 Hz), 8.65 (s, 1H Ar-*H*).

2-(3,4-Dimethoxyphenyl)-4-(4-phenylphenyl)-1,3-selenazole (14)

Yield: 73%. M.p. 160-161 °C. Anal. Calc. for $C_{23}H_{19}NO_2Se$: C, 65.72; H, 4.56; N, 3.30. Found: C, 65.24; H, 4.51; N, 3.30%. ^{1}H NMR (DMSO-d_6): δ 3.90(s, 6H, *OCH_3*), 7.12 (d, 1H, Ar-*H*, *J*= 8.24 Hz), 7.33-7.65 (m, 3H, Ar-*H*), 7.67-8.45 (m, 8H, Ar-*H*), 8.65 (s, 1H, Ar-*H*).

2-(4-(Methylthio)phenyl)-4-(4-bromophenyl)-1,3-selenazole (15)

Yield: 61%. M.p. 172-173 °C. Anal. Calc. for $C_{16}H_{12}BrNSSe$: C, 46.96; H, 2.96; N, 3.42. Found: C, 46.74; H, 2.86; N, 3.34%.

2-(4-(Methylthio)phenyl)-4-(4-phenylphenyl)-1,3-selenazole (16)

Yield: 53%. M.p. 194-196 °C. Anal. Calc. for $C_{22}H_{17}NSSe$: C, 65.02; H, 4.22; N, 3.45. Found: C, 64.95; H, 3.88; N, 3.34%. ^{1}H NMR (DMSO-d_6): δ 2.52 (s, 3H, *SCH_3*), 7.60-7.25(m, 5H, Ar-*H*), 7.77 (d, 4H, Ar-*H*, *J*=8.25 Hz), 8.18-7.84 (m, 4H, Ar-*H*), 8.70 (s, 1H, Ar-*H*).

2-(6-Methoxy-2-naphthyl)-4-(4-phenylphenyl)-1,3-selenazole (17)

Yield: 59%. M.p. 249-250 °C. Anal. Calc. for $C_{26}H_{19}NOSe$: C, 70.91; H, 4.35; N, 3.18. Found: C, 71.23; H, 4.41; N, 3.34%. ^{1}H NMR (DMSO-d_6): δ 2.52 (s, 3H, *OCH_3*), 7.60-7.25 (m, 5H, Ar-*H*), 7.80 (d, 4H, Ar-*H, J*=7.96 Hz), 8.22-7.88 (m, 4H, Ar-*H*), 8.70 (s, 1H, Ar-*H*).

MS: m/z: 441(M^+).

2-(6-Methoxy-2-naphthyl)-4-(4-bromophenyl)-1,3-selenazole (18)

Yield: 62%. M.p. 110 °C. Anal. Calc. for $C_{20}H_{14}BrNOSe$: C, 54.20; H, 3.18; N, 3.16.

Found: C, 54.66; H, 3.34; N, 3.25%. 1H NMR ($CDCl_3$): 3.83 (s, 3H, *OCH_3*), 6.86 (dd, 1H, Ar-*H, J*=2.10, 8.42 Hz), 7.20 (d, 1H, Ar-*H*, *J*=7.9 Hz), 7.45 (d, 2H, Ar-*H*, *J*=8.41 Hz), 7.82-8.10 (m, 3H, Ar-*H*), 8.11 (s, 1H, Ar-*H*), 8.13-8.37 (m, 3H, Ar-*H*).

2-(6-Methoxy-2-naphthyl)-4-phenyl-1,3-selenazole (19)

Yield: 70%. M.p. 189-190 °C. Anal. Calc. for $C_{20}H_{15}BrNOSe$: C, 65.94; H, 4.15; N, 3.84. Found: C, 65.65; H, 4.06; N, 3.80%. ^{1}H NMR ($CDCl_3$): 3.95 (s, 3H, *OCH_3*), 7.17(dd, 1H, Ar-*H, J*=1.72, 8.50 Hz), 7.21(d, 1H, Ar-*H, J*=8.32 Hz), 7.38-7.32 (m, 1H, Ar-*H*), 7.48-7.42(m, 2H, Ar-*H*), 7.79(d, 1H, Ar-*H*, *J*=8.48Hz), 7.89(d, 1H, Ar-*H*, *J*=8.80Hz), 8.06-8.01(m, 2H, Ar-*H*), 8.09(s, 1H, Ar-*H*), 8.08(dd, 1H, Ar-*H*, *J*=1.80, 8.14 Hz), 8.36(d, 1H, Ar-*H*, *J*=7.92 Hz). ^{13}C NMR($CDCl_3$): 55.4, 105.9, 117.8, 119.7, 125.1, 126.5, 126.8, 127.4, 127.9, 128.7, 130.2, 131.9, 135.5, 135.7, 157.0, 158.7, 174.3.

2-(4-Methoxy-1-naphthyl)-4-phenyl-1,3-selenazole (20)

Yield: 40%. Yellow oil. Anal. Calc. for $C_{20}H_{15}BrNOSe$: C, 65.94; H, 4.15; N, 3.84. Found: C, 66.05; H, 4.23; N, 4.01%. ^{1}H NMR ($CDCl_3$): 3.96(s, 3H, *OCH_3*), 6.68(d, 1H, Ar-*H*, *J*=7.85 Hz), 7.23-7.61(m, 8H, Ar-*H*), 7.75(d, 1H, Ar-*H*, *J*=7.83 Hz), 8.10(s, 1H, Ar-*H*), 8.22(d, 1H, Ar-*H*, *J*=8.22 Hz).

2-(4-phenylphenyl)-4-(4-bromophenyl)-1,3-selenazole (21)

Yield: 21%. M.p. 203-205 °C. Anal. Calc. for $C_{21}H_{14}BrNSe$: C, 57.43; H, 3.21; N, 3.19. Found: C, 57.22; H, 3.00, N, 3.12%. ^{1}H NMR (DMSO-d_6): 7.52 (d, 2H, Ar-*H*, *J*=7.45 Hz), 7.77-7.95 (m, 7H, Ar-*H*), 7.95-6.25 (m, 4H, Ar-*H*), 8,80 (s, 1H, Ar-*H*).

2,4-Bis(4-phenylphenyl)-1,3-selenazole (22)

Yield: 42%. M.p. 255-257 °C. Anal. Calc. for

$C_{27}H_{19}NSe$: C, 74.31; H, 4.39; N, 3.21. Found: C, 73.73; H, 4.41; N, 3.30%. ^{1}H NMR (DMSO-d_6): 7.27-7.72(m, 14H, Ar-*H*), 7.84(d, 2H, Ar-*H, J*= 8.07 Hz), 8.09(d, 2H, Ar-*H, J*=8.10 Hz), 8.58(s, 1H, Ar-*H*).

2,4-Bis(4-(methylthio)phenyl)-1,3-selenazole (23)

Yield: 35%. M.p. 121-122 °C. Anal. Calc. for $C_{17}H_{15}NS_2Se$: C, 54.25; H, 4.02; N, 3.72. Found: C, 53.83; H, 4.01; N, 3.30%. ^{1}H NMR (DMSO-d_6): δ 1.68 (s, 3H, SCH_3), 2..52 (s, 3H, SCH_3) 7.90-.27 (m, 8H, Ar-*H*), 8.00 (s, 1H, Ar-*H*).

2-phenyl-4-(4-bromophenyl)-1,3-selenazole (24)

Yield: 75%. M.p. 129-131 °C. Anal. Calc. for $C_{15}H_{10}BrNSe$: C, 49.62; H, 2.78; N, 3.86. Found: C, 49.83; H, 2.64; N, 3.70%. ^{1}H NMR (DMSO-d_6): δ 7.21 (d, 2H, Ar-*H, J*=8.40 Hz), 7.90-7.27 (m, 7H, Ar-*H*), 8.00 (s, 1H Ar-*H*).

MS: m/z: 363/365(M^+).

Oxidative addition reactions of 2,4-diaryl-1,3-selenazoles

Synthesis of 1,1-dichloro-2,4-diaryl-1,3-selenazoles

To a solution of 2,4-diaryl-1,3-selenazole (1.0 mmol) in dry diethyl ether (25 cm^3), sulfuryl chloride (0.70 ml) was added dropwise with stirring at 5 °C. The reaction mixture was allowed to stand at room temperature for 4 h. Concentration under reduce pressure and addition of hexane afforded the colourless to pale yellow solid compounds.

Compounds **25**, **33**, **39** and **42** were prepared by the same above method, see *Table* 1.

Synthesis of 1,1-dibromo-2,4-diaryl-1,3-selenazoles

These compounds were prepared by the following method:

2-(3,4-Dimethoxy phenyl)-4-(4-phenylphenyl)-1.3-selenazole (0.70 g; 1.5 mmol) dissolved in diethyl ether (10 cm^3) and a solution of bromine (0.25 cm^3, 1.5 mmol) in the same solvent was slowly added with stirring. A yellow precipitate was formed, which after 4 h was collected and recrystallized from ethanol/chloroform (4:1) to give 1,1-dibromo-2-(4,5-Dimethoxy phenyl)-4-(4-phenylphenyl)-1.3-selenazole(**26**) as yellow crystal, m.p. 156-157 °C.

Compounds **28**, **30**, **34**, **36** and **40** were prepared by the above method (*Table* 1).

Synthesis of 1,1-diiodo-2,4-diaryl-1,3-selenazoles

All diiodo derivatives were prepared according to the following method:

Iodine (0.39 g; 1.5 mmol) in dry diethyl ether (10 cm^3) was added dropwise to a solution of 2-(3,4-dimethoxy phenyl)-4-(4-phenylphenyl)-1,3-selenszole (0.70 g; 1.5 mmol) in dry diethyl ether (10 cm^3) with stirring at room temperature. A brown precipitate gradually formed which after 3 h, was collected by filtration and recrystallized from ethanol to give 1,1-diiodo-2-(3,4-dimethoxy phenyl)-4-(4-phenylphenyl)-1,3-selenszole (**27**) as yellow crystals, m.p. 136-139 °C.

Compounds **29**, **31**, **32**, **35**, **37**, **41**and **43** were prepared by the same above method, *Table* 1.

Synthesis of 1-ethyl-1-diiodo-2,4-diaryl-1,3-selenazolium(35)

An excess of freshly distilled ethyl iodide (2.0 cm^3) was added slowly with stirring at room temperature to the solution of **9** (0.41 g; 1 mmol) in diethyl ether (20 cm^3). After stirring for 4 h at room temperature, a light yellow solid separated which was filtered, dried and recrystallized with DMF/water to give **35** in 81% yield. M.p. 144-146 °C.

RESULTS AND DISCUSSION

Synthesis

The reaction of several primary arylselenocarboxamides with 4-bromo- and 4-phenylphenacyl bromides gave the corresponding 2,4-diaryl-1,3-selenazoles in good yields (Experimental section). All selenazoles (**1-24**) are yellow to white crystalline solids with sharp melting point which are soluble in common organic solvents. The IR spectra of all compounds show an absorption band between 1580-1630 cm^{-1} due to ν(C=N) and an absorption band in range 595-560 cm^{-1} may assigned to ν(Se-C).[4a,13,14] ^{1}H NMR spectra of compounds **1-24** were recorded in DMSO-d_6 or $CDCl_3$ and gave a further support for the formation of these compounds. The ^{1}H NMR spectra consist of, in addition to SCH_3/OCH_3/OCH_2CH_3, low field signals of aryl protons at the range 6.18-8.82 ppm (Experimental section).

The 2,4-diaryl-1,3-selenazoles (**1-24**) are readily oxidized by SO_2Cl_2, Br_2 and I_2 to the corresponding

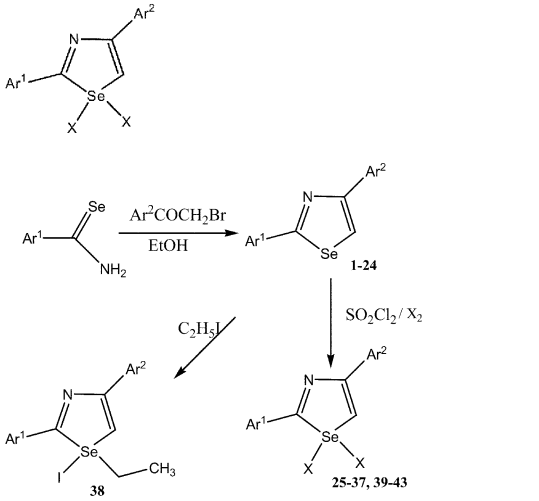
Table 1. Physical and Analytical data for 1,1-dihalo-2,4-diaryl-1,3-selenazoles*

No	Ar^1	Ar^2	X	Yield (%)	M.p. (°C)	Analysis[a] C	H	N	^{1}H NMR
25	3,4-$(MeO)_2C_6H_3$	4-PhC_6H_4	Cl	70	143-145	56.61 (56.82)	4.45 (4.57)	2.52 (2.76)	3.98(s, 3H,.OCH_3); 4.04(s, 3H,OCH_3); 6.92(d,1H,Ar*H, J*=7.65); 7.26(s,1H,Ar*H*); 7.39(d, 2H, Ar*H, J*=7.54 Hz); 7.44-7.53(m, 4H, Ar*H*); 7.65(d, 2H, Ar*H, J*=8.22 Hz); 7.95(d, 1H, Ar*H*, *J*=8.02 Hz); 8.07(d, 2H, Ar*H, J*=8.12 Hz).
26	3,4-$(MeO)_2C_6H_3$	4-PhC_6H_4	Br	74	156-157	47.30 (47.61)	3.18 (3.30)	2.04 (2.41)	3.94(s, 3H, OCH_3); 3.97(s, 3H, OCH_3); 6.90(d, 1H, Ar*H, J*=7.76 Hz); 7.25(s, 1H, Ar*H*); 7.34-7.38 (m, 2H, Ar*H*); 7.50 (d, 1H, Ar*H, J*=7.96 Hz); 7.66(d, 2H, Ar*H, J*=8.20 Hz); 7.71 (d,2H, Ar*H, J*=8.02 Hz); 8.05(d, 2H, Ar*H, J*=7.97 Hz).
27	3,4-$(MeO)_2C_6H_3$	4-PhC_6H_4	I	67	136-139	40.65 (40.98)	2.71 (2.84)	1.85 (2.08)	3.88(s, 3H.OCH_3); 3.95(s, 3H, OCH_3); 6.85(d, 1H, Ar*H, J*=7.75 Hz); 7.19(s, 1H, Ar*H*); 7.36(d, 2H, Ar*H, J*=8.25 Hz), 7.40-7.42(m, 4H, Ar*H*); 7.57(d, 1H, Ar*H*, *J*=7.90 Hz), 7.62(s, 1H, Ar*H*); 8.01(d, 2H, Ar*H, J*=8.02 Hz).
28	3,4-$(MeO)_2C_6H_3$	4-BrC_6H_4	Br	75	155-157	34.74 (35.00)	2.12 (2.40)	2.08 (2.40)	3.89(s, 3H, OCH_3); 3.94(s, 3H, OCH_3); 7.39(d, 1H, Ar*H*); 7.45-7.55(m, 3H, Ar*H*); 7.78(d,2H, Ar*H, J*=7.86 Hz); 7.96(s, 1H, Ar*H*).
29	3,4-$(MeO)_2C_6H_3$	4-BrC_6H_4	I	79	159-161	29.89 (30.16)	1.88 (2.08)	2.00 (2.07)	3.94(s, 3H, OCH_3); 4.00(s, 3H, *O*CH_3); 6.90(d, 1H, Ar*H*, *J*=7.58 Hz); 7.45-7.49(m, 1H, Ar*H*); 7.53-7.59(m,3H, Ar*H*); 7.86(d,2H Ar*H*, *J*=7.68 Hz); 8.02(s, 1H, Ar*H*).
30	4-BrC_6H_4	4-BrC_6H_4	Br	78	137-139	29.63 (29.92)	1.25 (1.49)	1.96 (2.32)	7.50-7.53(m, 4H, Ar*H*); 7.77-7.90(m,4H, Ar*H*); 8.05(s, 1H, Ar*H*).
31	4-BrC_6H_4	4-BrC_6H_4	I	82	142-146	25.77 (25.89)	1.17 (1.30)	1.87 (2.01)	7.53-7.59(m, 4H, Ar*H*); 7.82-7.87 (m,4H, Ar*H*); 8.11(s, 1H, Ar*H*).
32	4-$EtOC_6H_4$	4-BrC_6H_4	I	68	153-155	30.67 (30.89)	1.95 (2.13)	1.78 (2.12)	1.45(t, 3H, CH_3); 4.08(q, 2H, CH_2); 6.92 (d, 2H Ar*H*, *J*=7.95 Hz); 7.54(d, 2H, Ar*H, J*=8.15 Hz); 7.85-7.82(m, 4H, Ar*H*); 8.01(s, 1H, Ar*H*).
33	2-$MeOC_6H_4$	4-BrC_6H_4	Cl	73	182-184	41.10 (41.41)	2.47 (2.61)	1.83 (3.02)	4.07(s,3H,OCH_3); 7,06(m, 2H Ar*H*); 7.26(s,1H, Ar*H*); 7.45(t, 1H, Ar*H*); 7.92(d, 2H, Ar*H*, *J*=7.88 Hz); 8.23(s, 1H, Ar*H*); 8.61(d, 2H, Ar*H*, *J*=8.18Hz).
34	2-$MeOC_6H_4$	4-BrC_6H_4	Br	69	138-140	34.56 (34.75)	1.97 (2.19)	2.01 (2.19)	4.02(s, 3H, OCH_3); 7,08(m, 2H, Ar*H*); 7.30(s,1H, Ar*H*); 7.47(t, 1H, Ar*H*); 7.82(d, 2H, Ar*H, J*=7.57 Hz); 8.20(s, 1H, Ar*H*); 8.56(d, 2H, Ar*H, J*=7.97 Hz).
35	2-$MeOC_6H_4$	4-BrC_6H_4	I	78	148-150[b]	29.39 (29.70)	1.69 (1.87)	1.78 (2.17)	4.01(s, 3H, OCH_3); 7,01(m, 2H); 7.32(m, 1H, Ar*H*); 7.49(d, 2H, Ar*H*, *J*=8.03 Hz); 7.86(d, 2H, A*H, J*=7.95 Hz); 8.12(s, 1H, Ar*H*); 8.51(d, 1H, Ar*H, J*=7.65 Hz).
36	4-$CH_3SC_6H_4$	4-PhC_6H_4	Br	71	130-132	46.43 (46.67)	3.03 (3.03)	2.23 (2.47)	2.54(s, 3H, SCH_3); 7.25(s, 1H, Ar*H*); 7.29(d, 2H, Ar*H*); 7.41(d, 2H, Ar*H, J*=7.97 Hz); 7.51(m, 1H, Ar*H*); 7.64-7.71(m, 3H, Ar*H*); 7.97(d, 2H, Ar*H*); 8.04(d, 2H, Ar*H*); 8.08(s, 1H, Ar*H*).
37	4-$CH_3SC_6H_4$	4-PhC_6H_4	I	77	140-142	39.64 (40.02)	2.43 (2.06)	1.83 (2.12)	2.45(s, 3H, SCH_3); 6.94-7.04(m, 2H, Ar*H*); 7.18-7.22(m,3H, 3H, Ar*H*); 7.39(m, 2H, Ar*H*); 7.58-7.64(m, 2H, Ar*H*); 7.86(d, 2H, Ar*H*, *J*=7.78 Hz); 8.01(d, 2H, Ar*H, J*=7.8, Hz); 8.03(s, 1H, Ar*H*).
38	4-$EtOC_6H_4$	4-BrC_6H_4	Et ,I	81	144-146	40.43 (40.52)	3.30 (3.40)	2.02 (2.49)	1.45(t, 3H, OCH_2CH_3); 1.69(t, 3H, $SeCH_2CH_3$); 2.10(q, 2H, $SeCH_2CH_3$); 4.09(q, 2H, $SeCH_2CH_3$); 6.95(d, 2H, Ar*H, J*=7.95 Hz); 7.55-7.62(m, 2H. Ar*H*); 7.80-7.95(m, 4H, Ar*H*); 8.02(s, 1H, Ar*H*).

Table 1. Continued

No	Ar^1	Ar^2	X	Yield (%)	M.p. (°C)	Analysis[a] C	H	N	^{1}H NMR
39#	4-$CH_3SC_6H_4$	C_6H_5	Cl	75	129-130	45.28 (45.65)	3.17 (3.38)	2.86 (3.13)	2.54(s, 3H, S*CH*$_3$); 7.26-7.31(m, 4H, Ar*H*); 7.56(d, 2H, Ar*H, J*=8.01 Hz); 7.85-7.89(m, 3H, Ar*H*); 8.07(s, 1H, Ar*H*).
40#	4-$CH_3SC_6H_4$	C_6H_5	Br	63	109-111	36.64 (36.84)	2.88 (3.09)	2.31 (2.53)	2.45(s, 3H, S*CH*$_3$); 7.19-7.23(m, 3H, Ar*H*); 7.49(m, 2H, Ar*H*); 7.67(d, 1H, Ar*H*, *J*=7.93 Hz); 7.76-7.83(m, 3H, Ar*H*); 8.01(s,1H, Ar*H*).
41#	4-$CH_3SC_6H_4$	C_6H_5	I	77	132-133	32.01 (32.40)	2.30 (2.40)	1.97 (2.22)	2.47(s, 3H, SCH$_3$); 7.19 (d, 2H, Ar*H*, *J*=8.05 Hz); 7.45(d, 2H, Ar*H*, *J*=7.78 Hz); 7.78-7.83(m, 5H, Ar*H*); 7.99(s, 1H, Ar*H*)
42	6-$MeOC_{10}H_6$	4-BrC_6H_4	Cl	75	141-143	46.73 (46.10)	2.24 (2.74)	2.51 (2.72)	3.92(s, 3H, *OCH*$_3$); 7.18(dd, 1H, Ar-*H, J*=1.65, 7.58 Hz); 7.22(d, 1H, Ar-*H*, *J*=7.74 Hz); 7.33-7.38(m, 1H, Ar-*H*); 7.39-7.48(m, 2H, Ar-*H*); 7.80 (d, 1H, Ar-H, *J*=8.41Hz); 8.11(d, 1H, Ar-H, *J*=8.52Hz); 8.03-8.08(m, 2H, Ar-*H*); 8.11(s, 1H, Ar-*H*); 8.18(dd, 1H, Ar-*H, J*=1.58, 7.85 Hz); 8.37 (d, 1H, Ar-*H*).
43	6-$MeOC_{10}H_6$	4-BrC_6H_4	I	78	161-163	34.61 (34.46)	2.22 (2.02)	1.56 (2.01)	3.91(s, 3H, *OCH*$_3$); 7.20(dd, 1H, Ar-*H, J*=2.40, 8.25 Hz), 7.24(d, 1H, Ar-*H, J*=7.80 Hz); 7.32-7.38(m, 1H, Ar-*H*); 7.42-7.50(m, 2H, Ar-*H*); 7.71(d, 1H, Ar-H, *J*=8.23Hz); 7.84(d, 1H, Ar-H, *J*=8.05Hz); 8.00-8.07(m, 2H, Ar-*H*); 8.12(s, 1H, Ar-*H*); 8.15(dd, 1H, Ar-*H, J*=1.8, 7.78 Hz); 8.39(d, 1H, Ar-*H, J*=7.93Hz).

*Ar^1 and Ar^2 as illustrated below[a]Calculated values are in parentheses. # Contains one or two H_2O molecules



Scheme 1. Preparative methods for compounds **1-43**.

Se(IV) dihalides (*i.e.* 1,1-dihalo-2,4-diaryl-1,3-selenazoles (**25-36** and **39-43**)), while the reaction of compound **9** with ethyl iodide gave the selenonium salt (**38**) in high yield (*Scheme* 1, *Table* 1). All these new compounds are stable toward moisture and air. They were characterized by IR, NMR, mass spectroscopic data and elemental analysis, (*Table* 1). The IR spectra of the dihalo derivatives are quite similar to those of the 2,4-diaryl-1,3-selenazoles(**1-24**) Thus, in the IR spectra of compounds **25-43**, a strong band appears in the region 1610-1580 cm^{-1} due to ν(C=N)[13,14], while the (C-Se) stretching vibration appeared in the region 590-570 cm^{-1}.[13,14] Furthermore, the (C-H) vibrations for the selenazole ring in compounds **1-43** is observed in the region 3070-3011 cm^{-1} which is characteristic of heteroaromatic compounds.[15]

^{1}H NMR spectra of compounds **25-43** were recorded in $CDCl_3$ solution and show all the expected protons with proper intensity ratio, *Table* 1.

The mass spectra of compounds **1**, **4**, **11**, **17** and **24** show the molecular ion with a correct isotope pattern for compounds containing selenium. The base peak of each spectrum was based on $ArCN^+$ which is corresponding to the loss of $ArC{=}CHSe^+$ ion. The dihalo derivatives (*i.e.* compounds **27**, **28**, **29**, **31**, **35**, **36** and **38**) show loss of halogens(X_2) in two steps from the parent ion. In general, the mass spectra of compounds **27**, **28**, **29**, **31**, **35**, **36** and **38** contain features characteristic of selenazole compounds, which show the exact fragmentation patterns.

Biological activity

***In vitro*-HIV assay**

The cavity on glycoprotein 41 (gp41) of the HIV plays an important rule in the viral replication process, which could hold a small molecule inhibitor, and heterocyclic compounds namely non-reverse transcriptase inhibitors (NNRTI's) that would fit this cavity have been identified and inhibit fusion.[16] Accordingly, our synthetic strategy for synthesis of the new heterocyclic derivatives namely 2,4-diaryl-1,3-selenazoles depend on this hypothesis. Compounds **26**, **32**, **33** and **37** were tested for their anti HIV-1 and HIV-2 activity, *in vitro*, using III_B and ROD strains, respectively, in human T-lymphocyte (MT-4) cells (T means the immune cells Thymus). The results are summarized in *Table* 2, in which the data have been included for comparison purpose. Compounds-induced cytotoxicity was also measured in MT-4 cell in parallel with the antiviral activity. Non of the selenazole derivatives were found to inhibit HIV-1 replication, *in vitro*, at EC_{50} lower than CC_{50} in comparison to the antiviral NNRTI's agents Efavirenz (EFV; 6-chloro-4-cyclopropyl-4-(trifluoromethyl)-1H-benzo[d][1,3]oxazin-2(4H)-one)[17] and Capravirin[(5-(3,5-dichlorophenylthio)-4-isopropyl-1-(pyridin-3-ylmethyl)-4,5-dihydro-1H-imidazol-2-yl)methyl carbamate],[18] except compound **32** which showed IC_{50} > 11.8 μg/ml against HIV-1 (III_B strain), and might lead to increase in activity on modification of the biofunctional group attached to the selenazole nucleous. The low Si<1 indicated no HIV selectivity.

In conclusion, the structure-activity relationship suggested that the substitution of selenazole bearing another heterocycle moiety such as thiazole group might increase the activity against the HIV through the increasing of the binding between the gp41 of the virus and the suggested new selenazole derivatives.

Crystal structure of 2-(3,4-dimethoxyphenyl)-4-(4-bromophenyl)-1,3-selenazole (13)

The absolute structure for 2-(3,4-dimethoxyphenyl)-4-(4-bromophenyl)-1,3-selenazole (**13**) was determined by using X-ray diffraction analysis (*Fig*. 1). A summary of crystal data and structure refinement for compound **13** is provided in *Table* 3. Selected bond lengths and angles are listed in *Table* 4. The lengths of C8-N and C9-N in **13** are 1.384(11)

Table 2. *In vitro* anti-HIV-1[a] and HIV-2[b] of some selenazole compounds

Compounds	Strain	CC_{50}(μg/ml)[c]	EC_{50}(μg/ml)[d]	SI[e]
26	IIIB	>15.3	15.30	<1
	ROD	>18.4	16.58	<1
32	IIIB	>**11.8**	11.8	<1
	ROD	>53.6	53.6	<1
33	IIIB	>87.1	87.1	<1
	ROD	>125	125	<1
37	IIIB	>125	125	<1
	ROD	>125	125	<1
EFV	IIIB	**40**	0.003	13333
Capravirin	IIIB	11	0.0014	76850

[a]Anti-HIV-1 activity measured with strain IIIB. [b]Anti-HIV-2 activity measured with ROD strain. [c]Compound concentration required to reduce the viability of mock-infected MT-4 cell by 50. [d]Compound concentration required to achieve 50% protection of MT-4 cell from the HIV-1 induced cytopathogenicity. [e]SI : Selectivity therapeutic index (IC_{50}/CC_{50})

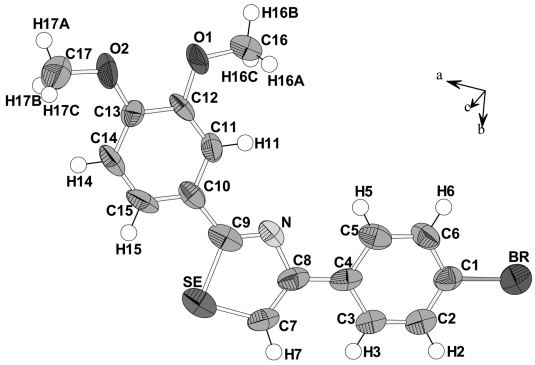


Fig. 1. Molecular structure of 2-(3,4-dimethoxyphenyl)-4-(4-bromophenyl)-1,3-selenazole. Thermal elipoids are drawn at the 50% probability level.

Å and 1.268(11) Å (*Tables* 4) which are shorter than the usual single bond length of 1.47 Å.[19,20] This is indicating clearly their double bond character. The sum of the three angles around each of the C8 and C9 atom is 360.0, respectively. This means that the arrangements of N, C8, C7 and C4, and N, C9, Se and C10 atom is planar,[20] respectively, *Table* 4.

Supplementary Information

Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre CCDC no. CCDC 648453 for compounds **13**. Further details of the crystal structure investigations are available free of charge via www.ccdc.cam.ac.uk/deposit (or from the CCDC,

Table 3. Crystal and structure refinement for compound **13**.

Crystal data	Mo Kα radiation
$C_{17}H_{14}BrNO_2Se$	λ = 0.71073 Å
Mr = 423.16	Cell parameters from 25 reflections
Orthorhombic	θ = 2.11-22.10°
Pb_{ca}	μ = 4.700 mm^{1}
a = 7.3626 (4) Å	T = 293 (2) K
b = 19.2762 (4) Å	Small plate
c = 23.2673 (4) Å	Colorlouss
V = 3302.2 (2) $Å^3$	0.30 × 0.15 × 0.04 mm
Z = 8	
D_x = 1.702 Mg m^{-3}	
D_m not measured	θ_{max} = 22.10°
	h = -1 → 7
Data collection	k = -1 → 20
diffractométre CAD-4 diffractometer	l = -1 → 24
ω/2θ scans	2 standard reflections
Absorption correction:	frequency: 120 min
ψ scan (North, Phillips & Mathews, 1968)	intensity decay: 2%
T_{min} = 0.755, T_{max} = 0.998	
2712 measured reflections	$w=1/[\sigma^2(F^2_o) + (0.0213P)^2 + 0.0000P]$
2028 independent reflections	where $P = (F_o^2 + 2F_c^2)/3$
811 reflections with	
>2sigma(I)	
R_{int} = 0.0695	
Refinement	$(\Delta/\sigma)_{max}$= 0.000
Refinement on F^2	$\Delta\rho_{max}$ = 0.320 e ρ^{-3}
$R[F^2 > 2\sigma(F^2)]$ = 0.0579	$\Delta\rho_{min}$ = 0.343 e $Å^{-3}$
$\omega R(F^2)$ = 0.0894	Extinction correction: SHELXL
S = 0.881	Extinction coefficient: 0.00017 (5)
2028 reflections	Scattering factors from International Tables
202 parameters	for Crystallography (Vol. C)
H atoms treated by a mixture of independent and constrained refinement	w=1/[_2(F_o^2) + (0.0213P)2 + 0.0000P]

Table 4. Selected geometric parameters (Å, °) for compound 13.

Se—C7	1.832 (10)	C6—C1—C2	119.8 (10)
Se—C9	1.898 (9)	C6—C1—Br	121.2 (9)
Br—C1	1.901 (10)	C2—C1—Br	119.0 (9)
C1—C6	1.361 (11)	C1—C2—C3	120.4 (11)
C1—C2	1.377 (11)	C2—C3—C4^{i}	122.5 (10)
C2—C3	1.378 (12)	C3ii—C4—C5^{iii}	114.7 (10)
C3—C4^{i}	1.403 (11)	C3ii—C4—C8	123.3 (10)
C4—C3^{ii}	1.403 (11)	C5iii—C4—C8	121.9 (11)
C4—C5^{iii}	1.404 (11)	C6iii—C5—C4^{iv}	123.0 (11)
C4—C8	1.453 (12)	C1—C6—C5^{iv}	119.6 (10)
C5—C6^{iii}	1.393 (12)	C8—C7—Se	111.8 (8)
C5—C4^{iv}	1.404 (11)	C7—C8—N	116.4 (11)
C6—C5^{iv}	1.393 (12)	C7—C8—C4	125.3 (10)
C7—C8	1.370 (12)	N—C8—C4	118.3 (10)
C8—N	1.384 (11)	N—C9—C10	124.3 (10)
C9—N	1.268 (11)	N—C9—Se	116.0 (9)
C9—C10	1.503 (13)	C10—C9—Se	119.7 (9)
C10—C15	1.368 (12)	C15—C10—C	11 118.7 (10)
C10—C11	1.392 (11)	C15—C10—C9	122.4 (10)
C11—C12^{iv}	1.382 (11)	C11—C10—C9	118.9 (10)
C12—O1	1.370 (10)	C12iv—C11—C10	120.7 (10)
C12—C13	1.371 (12)	O1—C12—C13	113.7 (10)
C12—C11^{iii}	1.382 (11)	O1—C12—C11^{iii}	125.8 (11)
C13—O2	1.378 (10)	C13—C12—C11^{iii}	120.5 (10)
C13—C14^{v}	1.385 (10)	C12—C13—O2	115.5 (10)
C14—C13^{vi}	1.385 (10)	C12—C13—C14^{v}	119.8 (10)
C14—C15^{vii}	1.406 (12)	O2—C13—C14^{v}	124.7 (11)
C15—C14^{viii}	1.406 (12)	C13vi—C14—C15^{vii}	119.3 (10)
C16—O1	1.411 (9)	C10—C15—C14^{viii}	121.0 (9)
C17—O2^{ix}	1.388 (10)	C9—N—C8	112.5 (10)
O2—C17^{ix}	1.388 (10)	C12—O1—C16	118.1 (8)
C7—Se—C9	83.3 (5)	C13—O2—C17^{ix}	119.8 (9)

Symmetry codes: (i) x 1, y, z; (ii) 1 + x, y, z; (iii) 1/2 + x, 3/2 y, 1 z; (iv) x 1/2, 3/2 y, 1 z; (v) x, 3/2 y, 1/2 + z; (vi) x, 3/2 y, z 1/2; (vii) 1/2 + x, y, 1/2 z; (viii) x 1/2, y, 1/2 z; (ix) x, 2 y, 1 z.

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