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Dearomatization of oxa- or selenadiazolopyridines with neutral nucleophiles as an efficient approach to pharmacologically relevant nitrogen compounds

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Experimental

All chemicals were of commercial grade and were used as purchased. Melting points were measured on a Stuart SMP20 apparatus. The ^{1}H and ^{13}C NMR spectroscopic data were recorded on Bruker AC-300 (at 300 MHz and 75 MHz respectively). Chemical shifts are reported in ppm downfield from TMS. HRMS spectra were recorded on a Bruker micrOTOF II mass spectrometer using ESI. IR spectra were recorded on a Bruker Alpha spectrometer, and the samples were prepared as KBr pellets. All reactions were monitored by TLC analysis using ALUGRAM SIL G/UV$_{254}$ plates, which were visualized by UV light. 6-Nitro-4-azabenzofuroxan **1** [S1] and 2,3-diamino-5-nitropyridine [S2] were prepared according to the previously described procedure.

[4-(6-Nitro-1-oxido-4,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyridin-7-yl)phenyl]amine (3a): (56% yield); m.p. 180-181ºC (dec); ^{1}H NMR (DMSO-d$_6$, 300.13 MHz, δ): 5.47 (s, 1H), 7.30 (d, 2H, J = 8.4 Hz), 7.43 (d, 2H, J = 8.1 Hz), 8.52 (s, 1H), 10.54 (br.s., 3H, NH+NH$_2$) ppm; ^{13}C NMR (DMSO-d$_6$, 75.47 MHz, δ): 37.00, 107.32, 122.71, 126.02, 129.38, 133.12, 134.97, 138.08, 150.12 ppm; IR (KBr): ν = 474, 581, 655, 823, 1020, 1242, 1310, 1498, 1589, 1639, 2577, 2845, 3041 cm^{-1}; HRMS (ESI): [C$_{131}$H$_9$N$_5$O$_4$ + H]$^+$ calc. 276.0727, found 276.0732.

[2-Methyl-4-(6-nitro-1-oxido-4,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyridin-7-yl)phenyl]amine (3b): (55% yield); m.p. 127-128ºC (dec); ^{1}H NMR (DMSO-d$_6$, 300.13 MHz, δ): 2.02 (s, 3H, CH$_3$), 5.20 (s, 1H), 6.56 (d, 1H, J = 8.4 Hz), 6.82-6.84 (m, 2H), 7.10 (br.s., 3H, NH+NH$_2$), 8.46 (s, 1H) ppm; ^{13}C NMR (DMSO-d$_6$, 75.47 MHz, δ): 17.33, 36.69, 107.79, 113.88, 121.19, 123.63, 126.19, 127.12, 129.30, 137.19, 146.31, 150.42 ppm; IR (KBr): ν = 440, 508, 660, 753, 820, 855, 1011, 1083, 1243, 1315, 1449, 1496, 1586, 1638, 1649, 2781, 3077, 3329, 3399 cm^{-1}; HRMS (ESI): [C$_{12}$H$_{11}$N$_5$O$_4$ + H]$^+$ calc. 290.0884, found 290.0891.

***N*,*N*-Dimethyl-4-(6-nitro-1-oxido-4,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyridin-7-yl)aniline (3c):** (76% yield); m.p. 185-186ºC; ^{1}H NMR (DMSO-d$_6$, 300.13 MHz, δ): 2.88 (s, 6H, 2CH$_3$), 5.28 (s, 1H), 6.67 (d, 2H, J = 8.6 Hz), 7.10 (d, 2H, J = 8.6 Hz), 8.45 (s, 1H) ppm; ^{13}C NMR (DMSO-d$_6$, 75.47 MHz, δ): 36.58, 39.98, 107.80, 112.24, 123.65, 126.78, 128.52, 137.52, 150.00, 150.47 ppm; IR (KBr): ν = 473, 683, 757, 820, 1010, 1077, 1158, 1235, 1310, 1482, 1528, 1578, 1637, 1649, 3306 cm^{-1}; HRMS (ESI): [C$_{13}$H$_{13}$N$_5$O$_4$ + H]$^+$ calc. 304.1040, found 304.1031.

1-(6-Nitro-1-oxido-4,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyridin-7-yl)-2-naphthol (3d): (51% yield); m.p. 154-155ºC; ^{1}H NMR (DMSO-d$_6$, 300.13 MHz, δ): 6.42 (s, 1H), 7.07 (d, 1H, J = 8.8 Hz), 7.36 (t, 1H, J = 7.3 Hz), 7.57 (t, 1H, J = 7.7 Hz), 7.75-7.83 (m, 2H), 8.39-8.53 (m, 2H),

10.22 (s, 1H), 11.70 (br.s., 1H) ppm; ^{13}C NMR (DMSO-d_6, 75.47 MHz, δ): 29.39, 108.39, 113.22, 118.00, 122.65, 122.94, 125.99, 126.66, 127.79, 128.22, 129.50, 130.03, 133.70, 137.60, 152.20, 153.76 ppm; IR (KBr): ν = 458, 562, 743, 819, 1008, 1058, 1231, 1314, 1437, 1489, 1583, 1653, 1701, 3283 cm^{-1}; HRMS (ESI): $[C_{15}H_{10}N_4O_5 + H]^+$ calc. 327.0724, found 327.0721.

6-Nitro-7-(1*H*-pyrazol-1-yl)-4,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyridine 1-oxide (4a): (30% yield); m.p. 168-169ºC (dec.); ^{1}H NMR (DMSO-d_6, 300.13 MHz, δ): 6.27 (s, 1H), 7.08 (s, 1H), 7.48 (s, 1H), 8.13 (s, 1H), 8.70 (s, 1H), 12.28 (br.s., 1H) ppm; ^{13}C NMR (DMSO-d_6, 75.47 MHz, δ): 49.88, 104.66, 104.95, 132.44, 133.30, 139.54, 140.77, 150.75 ppm; IR (KBr): ν = 473, 560, 769, 806, 1012, 1056, 1088, 1171, 1238, 1316, 1490, 1588, 1645, 3092, 3122 cm^{-1}; HRMS (ESI): $[C_8H_6N_6O_4 + Na]^+$ calc. 273.0343, found 273.0349.

7-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-6-nitro-4,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyridine 1-oxide (4b): (65% yield); m.p. 179-180ºC (dec); ^{1}H NMR (DMSO-d_6, 300.13 MHz, δ): 2.01 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 5.82 (s, 1H), 6.89 (s, 1H), 8.71 (s, 1H), 12.18 (br.s., 1H) ppm; ^{13}C NMR (DMSO-d_6, 75.47 MHz, δ): 10.48, 13.38, 46.38, 104.54, 106.09, 124.00, 139.64, 141.34, 148.49, 150.76 ppm; HRMS (ESI): $[C_{10}H_{10}N_6O_4 + Na]^+$ calc. 301.0656, found 301.0642.

[3,5-Dimethyl-1-(6-nitro-1-oxido-4,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyridin-7-yl)-1*H*-pyrazol-4-yl]acetic acid (4c): (51% yield); m.p. 169-170ºC (dec); ^{1}H NMR (DMSO-d_6, 300.13 MHz, δ): 1.97 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.27 (s, 2H, CH_2), 6.91 (s, 1H), 8.69 (s, 1H), 12.19 (br.s., 2H, NH+COOH) ppm; ^{13}C NMR (DMSO-d_6, 75.47 MHz, δ): 9.14, 11.82, 28.83, 46.53, 106.06, 109.32, 124.06, 139.25, 139.56, 148.12, 150.74, 172.37 ppm; IR (KBr): ν = 461, 672, 756, 821, 857, 929, 1010, 1088, 1172, 1206, 1240, 1315, 1435, 1491, 1589, 1649, 1694, 1958, 2514, 3006, 3089, 3128, 3188 cm^{-1}; HRMS (ESI): $[C_{12}H_{12}N_6O_6 + H]^+$ calc. 359.0711, found 359.0713.

7-(4-Formyl-1*H*-pyrazol-1-yl)-6-nitro-4,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyridine 1-oxide (4e): (43% yield); m.p. 145-146ºC (dec); ^{1}H NMR (DMSO-d_6, 300.13 MHz, δ): 7.24 (s, 1H), 8.03 (s, 1H), 8.74 (s, 1H), 8.96 (s, 1H), 9.84 (s, 1H), 12.53 (br.s., 1H, NH) ppm; HRMS (ESI): $[C_9H_6N_6O_5 + H]^+$ calc. 279.0472, found 279.0471.

6-Nitro-7-(1*H*-1,2,4-triazol-1-yl)-4,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyridine 1-oxide (4f): (32% yield); m.p. 165ºC (dec); ^{1}H NMR (DMSO-d_6, 300.13 MHz, δ): 7.30 (s, 1H), 8.00 (s, 1H), 8.77 (s, 1H), 8.99 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 75.47 MHz, δ): 48.26, 104.90, 122.42, 140.73, 145.95, 150.81, 152.49 ppm; IR (KBr): ν = 475, 672, 971, 1014, 1088, 1136, 1239, 1318, 1422, 1484, 1581, 1656, 2746, 3077 cm^{-1}; HRMS (ESI): $[C_7H_5N_7O_4 + Na]^+$ calc. 274.0295, found 274.0290.

3-Hydroxy-5,5-dimethyl-2-(6-nitro-4,7-dihydro[1,2,5]selenadiazolo[3,4-*b*]pyridin-7-yl)-cyclohex-2-en-1-one (5a): (73% yield); m.p. 231-232ºC; ^{1}H NMR (DMSO-d_6, 300.13 MHz, δ): 0.93 (s, 6H, $2CH_3$), 2.19 (br.s., 4H, $2CH_2$), 5.67 (s, 1H), 8.12 (d, 1H, J = 6.2 Hz), 11.18 (br.d., 1H, J = 6.1 Hz, NH) ppm; ^{13}C NMR (DMSO-d_6, 75.47 MHz, δ): 27.57, 31.63, 36.19, 115.43, 125.80, 127.38, 136.81, 149.06, 151.87, 156.96 ppm; IR (KBr): ν = 420, 476, 725, 1029, 1085, 1213, 1256, 1296, 1381, 1474, 1491, 1577, 1636, 1701, 2928, 2959, 3055, 3126, 3189 cm^{-1}; HRMS (ESI): $[C_{13}H_{14}N_4O_4Se + H]^+$ calc. 371.0254, found 371.0249.

1,3-Dimethyl-5-(6-nitro-4,7-dihydro[1,2,5]selenadiazolo[3,4-*b*]pyridin-7-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (5b): (75% yield); m.p. 215-216ºC; ^{1}H NMR (DMSO-d_6, 300.13 MHz,

δ): 2.99 (s, 3H, CH_3), 3.17 (s., 3H, CH_3), 4.53 (s, 1H), 5.40 (s, 1H), 8.34 (d, 1H, J = 5.3 Hz), 11.42 (br.s., 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75.47 MHz, δ): 27.83, 28.22, 42.75, 52.97, 123.47, 139.27, 151.00, 151.08, 153.73, 166.55, 166.96 ppm; IR (KBr): ν = 412, 492, 561, 753, 825, 1100, 1215, 1244, 1272, 1303, 1386, 1423, 1460, 1578, 1639, 1670, 1688, 3267 cm^{-1}; HRMS (ESI): $[C_{11}H_{10}N_6O_5Se + Na]^+$ calc. 408.9771, found 408.9784.

3-(6-Nitro-4,7-dihydro[1,2,5]selenadiazolo[3,4-*b*]pyridin-7-yl)pentane-2,4-dione (5c): (95% yield); m.p. 188-189ºC; ^{1}H NMR (DMSO-d_6, 300.13 MHz, δ): 2.02 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.84 (d, 1H, J = 2.3 Hz), 5.19 (d, 1H, J = 2.3 Hz), 8.24 (s, 1H), 11.48 (br.s., 1H. NH) ppm; ^{13}C NMR (DMSO-d_6, 75.47 MHz, δ): 29.36, 31.03, 68.03, 123.46, 139.02, 151.57, 154.27, 203.49, 205.10 ppm; IR (KBr): ν = 522, 729, 1106, 1170, 1223, 1272, 1303, 1465, 1584, 1641, 1716, 3124, 3187 cm^{-1}; HRMS (ESI): $[C_{10}H_{10}N_4O_4Se + Na]^+$ calc. 352.9760, found 352.9751.

(6-Nitro-4,7-dihydro[1,2,5]selenadiazolo[3,4-*b*]pyridin-7-yl)malononitrile (5d): (45% yield); m.p. 171-172ºC; ^{1}H NMR (DMSO-d_6, 300.13 MHz, δ): 5.37 (s, 1H), 5.47 (s, 1H), 8.58 (s, 1H), 11.89 (br.s., 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75.47 MHz, δ): 28.74, 43.94, 113.68, 113.77, 121.29, 141.63, 150.65, 152.02 ppm; IR (KBr): ν = 520, 580, 737, 1104, 1227, 1262, 1302, 1459, 1579, 1362, 2924, 2967, 3113, 3223 cm^{-1}; HRMS (ESI): $[C_8H_4N_6O_2Se + Na]^+$ calc. 318.9453, found 318.9453.

***N*,*N*-Dimethyl-4-(6-nitro-4,7-dihydro[1,2,5]selenadiazolo[3,4-*b*]pyridin-7-yl)aniline (5e):** (45% yield); m.p. 257-258ºC; ^{1}H NMR (DMSO-d_6, 300.13 MHz, δ): 2.85 (s, 6H, $2CH_3$), 5.53 (s, 1H), 6.56 (d, 2H, J = 8.1 Hz), 7.08 (d, 2H, J = 8.0 Hz), 8.40 (s, 1H), 11.42 (br.s., 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75.47 MHz, δ): 46.31, 112.56, 126.70, 127.62, 129.52, 136.99, 149.53, 150.64, 155.80 ppm; IR (KBr): ν = 508, 581, 732, 797, 1099, 1226, 1259, 1286, 1465, 1525, 1575, 1620, 2967, 3113, 3171 cm^{-1}; HRMS (ESI): $[C_{13}H_{13}N_5O_2Se + H]^+$ calc. 352.0308, found 352.0311.

7-(5-Methoxy-1*H*-indol-3-yl)-6-nitro-4,7-dihydro[1,2,5]selenadiazolo[3,4-*b*]pyridine (5f): (77% yield); m.p. 215-216ºC; ^{1}H NMR (DMSO-d_6, 300.13 MHz, δ): 3.72 (s, 3H, CH_3), 5.89 (s., 1H), 6.73 (d, 1H, J = 8.7 Hz), 6.89 (s, 1H), 7.22-7.25 (m, 2H), 8.38 (s, 1H), 10.84 (br.s., 1H, NH), 11.50 (br.s., 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75.47 MHz, δ): 39.14, 55.23, 100.47, 110.84, 112.25, 114.71, 123.71, 125.50, 126.34, 131.47, 136.21, 150.91, 153.14, 155.48, 198.32 ppm; IR (KBr): ν = 429, 492, 569, 758, 1057, 1217, 1246, 1286, 1466, 1486, 1573, 1626, 2928, 3115, 3176, 3422 cm^{-1}; HRMS (ESI): $[C_{14}H_{11}N_5O_3Se + H]^+$ calc. 377.9957, found 377.9960.

7-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-6-nitro-4,7-dihydro[1,2,5]selenadiazolo[3,4-*b*]pyridine (5g): (62% yield); m.p. 194-195ºC (dec); ^{1}H NMR (DMSO-d_6, 300.13 MHz, δ): 1.92 (s, 3H, CH_3), 2.49 (s., 3H, CH_3), 5.76 (s, 1H), 6.86 (s, 1H), 8.53 (s, 1H), 11.82 (br.s., 1H, NH) ppm; IR (KBr): ν = 515, 735, 806, 862, 1097, 1236, 1302‘ 1420, 1487, 1578, 1637, 2714, 2780 cm^{-1}; HRMS (ESI): $[C_{10}H_{10}N_6O_2Se + Na]^+$ calc. 348.9923, found 348.9924.

References

S1. A. M. Starosotnikov, D. V. Shkaev, M. A. Bastrakov, I. V. Fedyanin, S. A. Shevelev and I. L. Dalinger, *Beilstein J. Org. Chem.*, 2017, **13**, 2854.

S2. S. Xiong Cai, J.-C. Huang, S. A. Espitia, M. Tran, V. I. Ilyin, J. E. Hawkinson, R. M. Woodward, E. Weber and J. F. W. Keana, *J. Med. Chem.*, 1997, **40**, 3679.

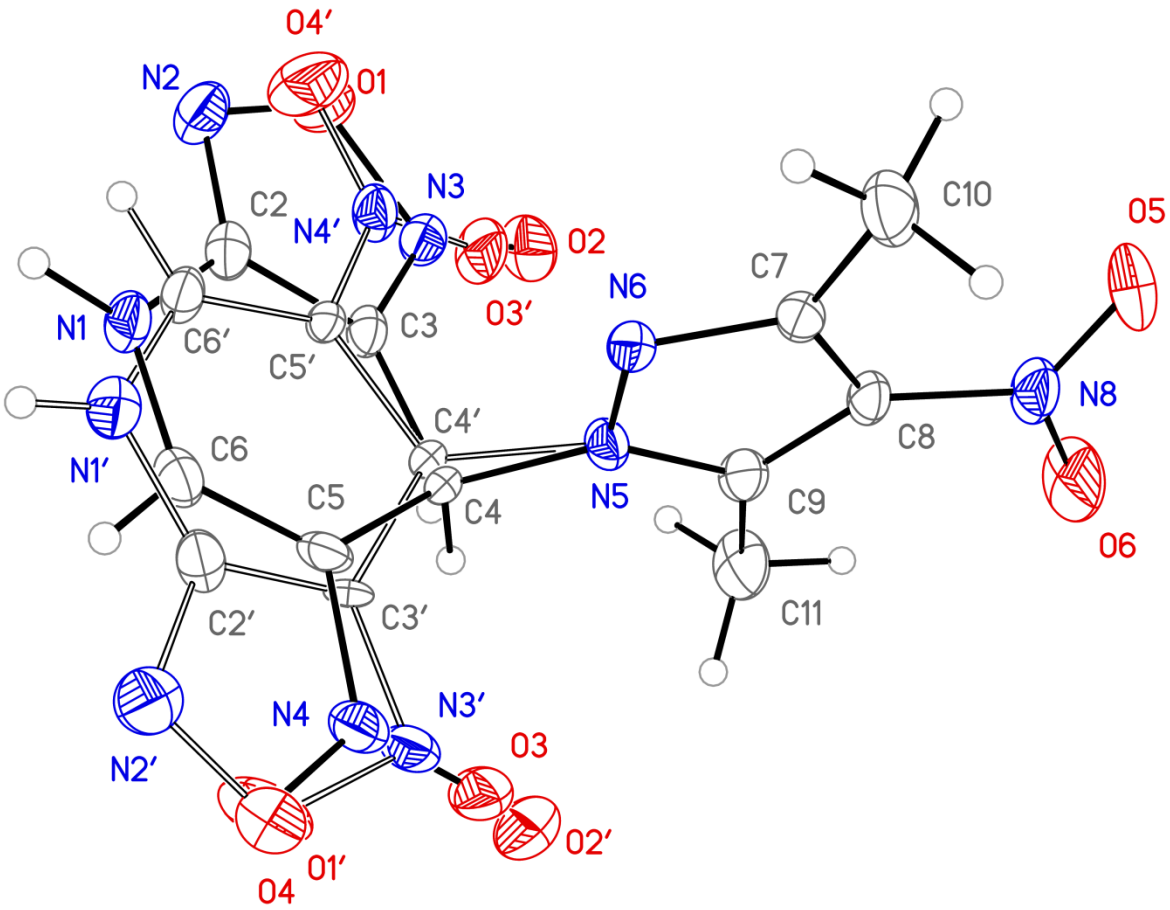

Figure S1 General view of the molecule **4d** in crystal with two overlapping disordered pyrido furoxan moieties. Anisotropic displacement parameters are drawn with 50% probability.

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) sd148

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No syntax errors found. CIF dictionary Interpreting this report

Datablock: sd148

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Bond precision:  C-C = 0.0020 A          Wavelength=0.71073

Cell:            a=13.2684(8)     b=7.2207(5)          c=13.7670(9)
                 alpha=90         beta=100.079(1)      gamma=90
Temperature:     120 K

                 Calculated                Reported
Volume           1298.62(15)               1298.62(15)
Space group      P 21/n                    P 21/n
Hall group       -P 2yn                    -P 2yn
Moiety formula   C10 H9 N7 O6              C10 H9 N7 O6
Sum formula      C10 H9 N7 O6              C10 H9 N7 O6
Mr               323.24                    323.24
Dx,g cm-3        1.653                     1.653
Z                4                         4
Mu (mm-1)        0.139                     0.139
F000             664.0                     664.0
F000'            664.36
h,k,lmax         18,10,19                  18,10,19
Nref             3783                      3783
Tmin,Tmax        0.955,0.967               0.818,0.862
Tmin'            0.955

Correction method= # Reported T Limits: Tmin=0.818 Tmax=0.862
AbsCorr = MULTI-SCAN

Data completeness= 1.000          Theta(max)= 30.000

R(reflections)= 0.0411( 2810)     wR2(reflections)= 0.0928( 3783)

S = 1.029                 Npar= 330
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The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

PLAT430_ALERT_2_B Short Inter D...A Contact O6 ..N2' 2.72 Ang.

Alert level C

PLAT906_ALERT_3_C Large K Value in the Analysis of Variance ..... 2.474 Check

Alert level G

PLAT003_ALERT_2_G Number of Uiso or Uij Restrained non-H Atoms ... 13 Report
PLAT171_ALERT_4_G The CIF-Embedded .res File Contains EADP Records 1 Report
PLAT186_ALERT_4_G The CIF-Embedded .res File Contains ISOR Records 1 Report
PLAT230_ALERT_2_G Hirshfeld Test Diff for C3 --C4 . 6.9 s.u.
PLAT301_ALERT_3_G Main Residue Disorder .....(Resd 1) 57% Note
PLAT395_ALERT_2_G Deviating X-O-Y Angle From 120 for O1 109.1 Degree
PLAT395_ALERT_2_G Deviating X-O-Y Angle From 120 for O1' 111.2 Degree
PLAT720_ALERT_4_G Number of Unusual/Non-Standard Labels ..... 2 Note
PLAT793_ALERT_4_G Model has Chirality at C4 (Centro SPGR) S Verify
PLAT811_ALERT_5_G No ADDSYM Analysis: Too Many Excluded Atoms .... ! Info
PLAT860_ALERT_3_G Number of Least-Squares Restraints ..... 78 Note
PLAT960_ALERT_3_G Number of Intensities with I < - 2*sig(I) ... 3 Check
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density. 7 Info

0 **ALERT level A** = Most likely a serious problem - resolve or explain
1 **ALERT level B** = A potentially serious problem, consider carefully
1 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
13 **ALERT level G** = General information/check it is not something unexpected

0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
6 ALERT type 2 Indicator that the structure model may be wrong or deficient
4 ALERT type 3 Indicator that the structure quality may be low
4 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check

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