Diselenide-derivative of 3-pyridinol targets redox enzymes leading to cell cycle deregulation and apoptosis in A549 cells

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Supplementary material

Experiment

Materials and Methods for synthesis

Se element (99.99 %), sodium borohydride ($NaBH_4$) and 2-bromo-3-pyridinol were purchased from commercial sources. All the reactions were done under an inert atmosphere of nitrogen. The solvents were purified by standard procedures and were distilled prior to use. The organoselenium compound was purified by recrystallization in hot water and methanol. Melting points was determined in capillary tube and was uncorrected. Elemental analysis was carried out on Flash EA 1112 Series CHNS Analyzer. NMR spectra were recorded on a Bruker Ascend^{TM}

400 MHz spectrometer operating at 400.13 (^{1}H), 100.61 (^{13}C{^{1}H}) and 76.31 MHz (^{77}Se{^{1}H}). ^{1}H and ^{13}C{^{1}H} NMR chemical shifts are relative to internal DMSO peak (δ = 2.5 ppm for ^{1}H and δ = 39.5 for ^{13}C{^{1}H} NMR). The ^{77}Se{^{1}H} NMR chemical shifts were relative to external standard diphenyl diselenide (Ph_2Se_2) in $CDCl_3$ (δ 463.0 ppm relative to Me_2Se (0 ppm)).

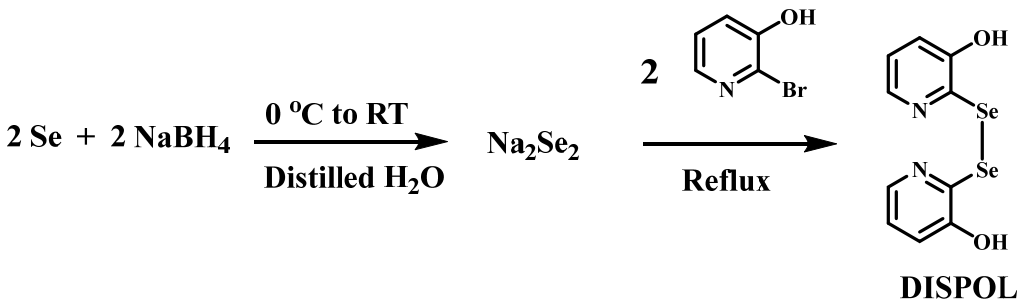
Synthesis of 2, 2′-diselenobis[3-pyridinol] $(SePyOH)_2$ or (DISPOL)

To an ice-cooled suspension of elemental Se (0.25 g, 3.165 mmol) in distilled water placed in a three-neck round bottom flask, a reducing agent, $NaBH_4$ (0.12 g, 3.165 mmol) was added slowly with stirring. As the reaction took place, slowly a dark red colored solution was formed which was then refluxed for 40 min and then allowed to cool down at room temperature. Further, 2-bromo-3-pyridinol (0.55 g, 3.165 mmol) was added slowly with vigorous stirring followed by refluxing the solution for 5 h whereupon a yellow-colored clear solution was formed. At this stage reflux was stopped and the obtained solution was filtered quickly through celite in a beaker and then allowed to cool to room temperature and kept undisturbed for overnight for crystallization. As a result, the orange yellow crystals of $(SePyOH)_2$ were obtained. The obtained crystalline $(SePyOH)_2$ was separated from the supernatant and washed with cold distilled water and then dried *in vacuo* to get the orange yellow compound (115 mg, 21%). This compound was recrystallized in hot methanol-water (90:10) mixture, to obtain the crystals. M.p. 185-186 °C (decomp.). Anal. Calcd. for $C_{10}H_8N_2O_2Se_2$: Calcd. C, 34.70; H, 2.33; N, 8.09%. Found: C, 33.94; H, 2.24; N, 7.89%. ^{1}H NMR (dmso-d_6) δ: 7.08 (dd, 1H), 7.12, 7.15 (each d, 1H), 7.95 (dd, 1H); ^{13}C{^{1}H} NMR (dmso-d_6) δ: 121.2, 123.7 (Se-*C*), 140.5, 141.1, 152.3 (HO-*C*) (py); ^{77}Se {^{1}H} NMR (dmso-d_6) δ: 389.0 ppm.

Reference

P. P. Phadnis, A. Kunwar, M. Kumar, R. Mishra, A. Wadawale, K. I. Priyadarsini and V. K. Jain (2017). Study of polymorphism in 2, 2′-diselenobis(3-pyridinol), J. Organomet. Chem. 852: 1-7.

Synthesis scheme



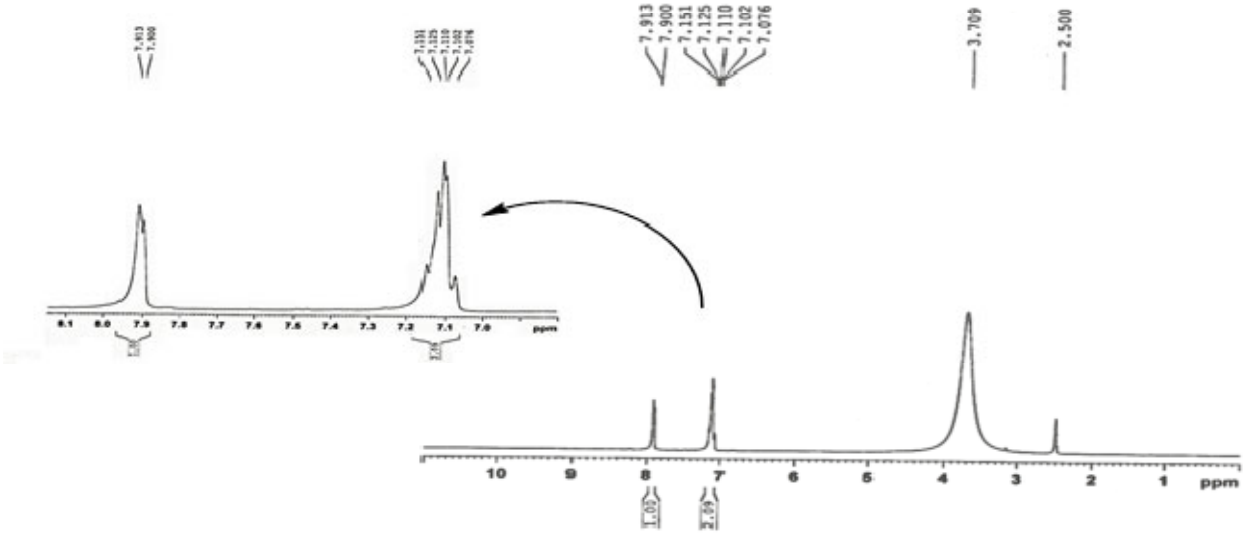


Figure S1. ^{1}H NMR of $(SePyOH)_2$ in dmso-d_6.

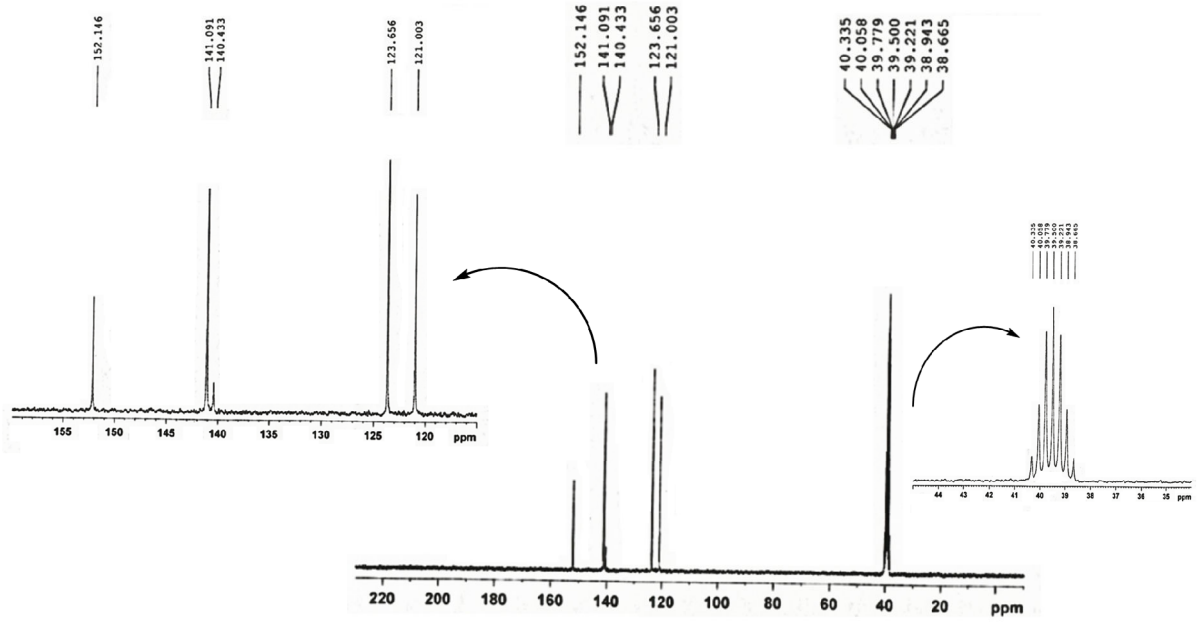


Figure S2. $^{13}C\{^{1}H\}$ NMR of $(SePyOH)_2$ in dmso-d_6

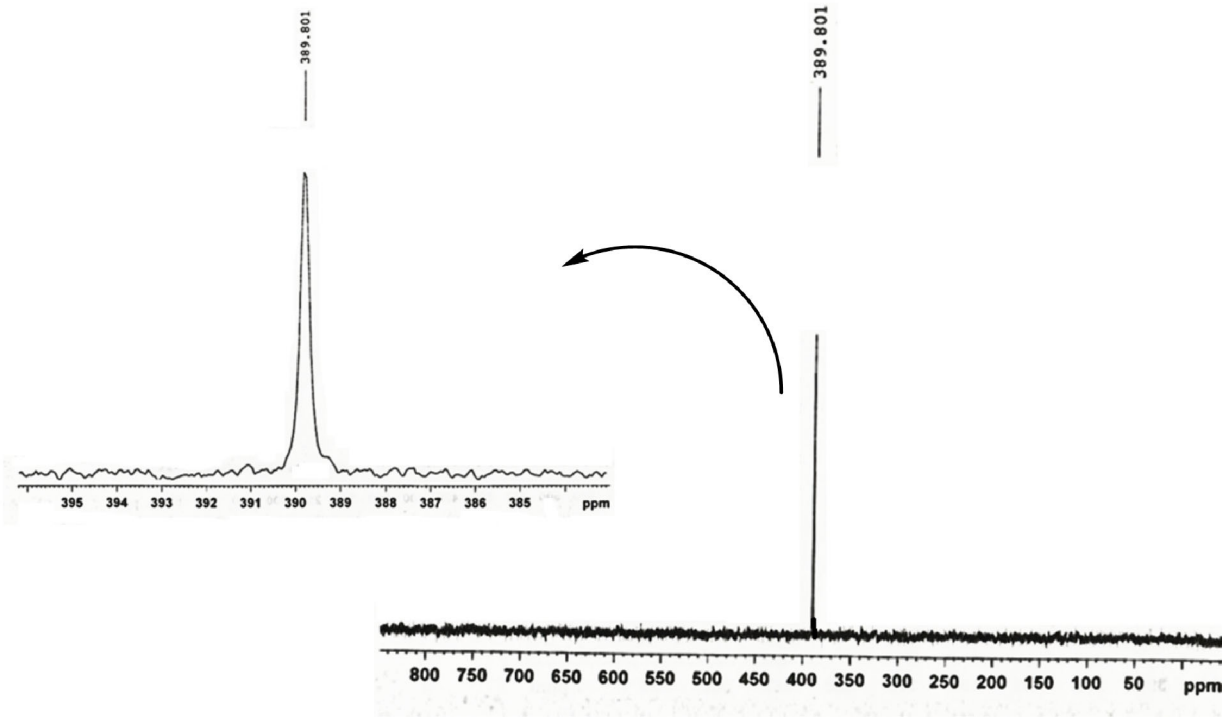


Figure S3. $^{77}Se\{^{1}H\}$) NMR of $(SePyOH)_2$ in dmso-d_6

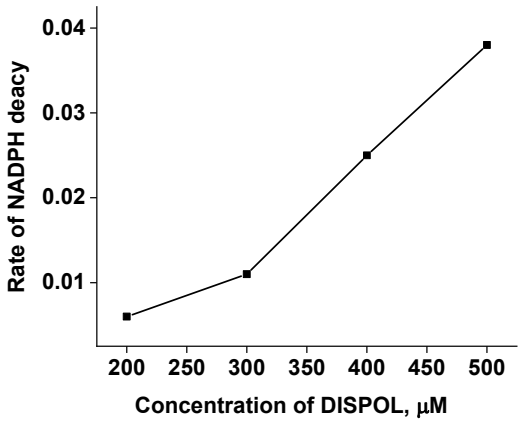


Figure S4. The plot of the rate of NADPH decay as function of the concentration of DISPOL in presence of rat liver TrxR. The absorbance of NADPH was monitored in 0.2 ml of 50 mM Tris–HCl, 1 mM EDTA buffer (pH 7.4) containing DISPOL (200–500 μM), 100 μM NADPH and 50 nM rat liver TrxR.

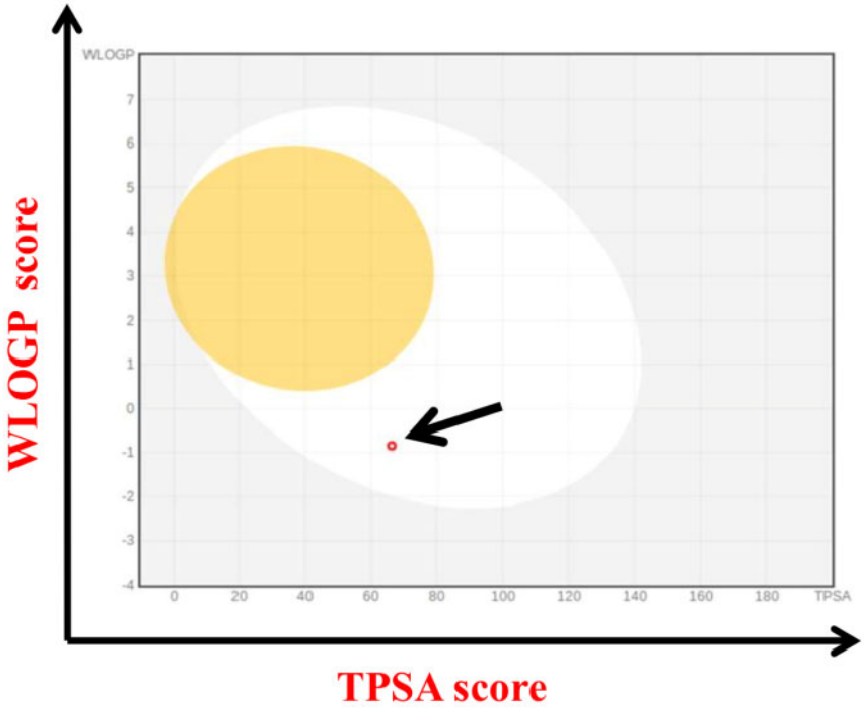


Figure S5. The BOILED-Egg Plot predicts gastrointestinal absorption and brain penetration of DISPOL by Swiss ADME software. The yolk region is the representative of the penetrance of a molecule in Blood Brain Barrier. The white region is the representative of the passive absorption of a molecule in the GI track. The arrows indicate the position of DISPOL. The red color of the dot indicates that DISPOL was not effluxed by BBB. WLOGP – Lipophilicity, TPSA – Topological surface area.