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# New cycloheptane nucleoside analogues

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### *Methods and Materials*

All reagents and solvents were purchased from Sigma-Aldrich, and used without further purification. Monitoring of the reactions was performed with using silica gel TLC plates (silica Merck 60 F254, visualization UV light at 254 and 365 nm). Column chromatography was performed on Merck Kieselgel 60–230 mesh (ASTM).
The microwave syntheses were performed with using a Discover® SP System by CEM Corp.
The catalytic hydrogenation processes were performed with using a Shaker Hydrogenation Apparatus by Parr Instrument Company.
$^1$H NMR spectra were recorded on a Varian Mercury Plus 400 instrument (400 MHz operating frequency) at 50$^o$C. Proton chemical shifts are reported in ppm (δ) referenced to solvent residual peak (DMSO-$d_6$ δ = 2.48 ppm) as an internal standard. *J* values are given in Hz.
LC–MS analysis was performed with a Surveyor MSQ instrument by Thermo Fisher Scientific. Chromatographic separation was done on a Phenomenex Onyx Monolithic C18 25×4.6 mm column using gradient elution. The column was maintained at ambient temperature. The elution program was as follows: gradient from 100% to 5% of mobile phase A (0.1% solution of formic acid in water) in mobile phase B (0.1% solution of formic acid in acetonitrile), with a flow rate of 1.5 mL min$^{-1}$. 2 μL of sample was injected into the system. UV spectra were recorded in the 200-800 nm range. Mass spectra were recorded using atmospheric pressure chemical ionization source in positive and negative polarities.

### 2-(But-3-enyl)-2-phenylhex-5-enenitrile (3)

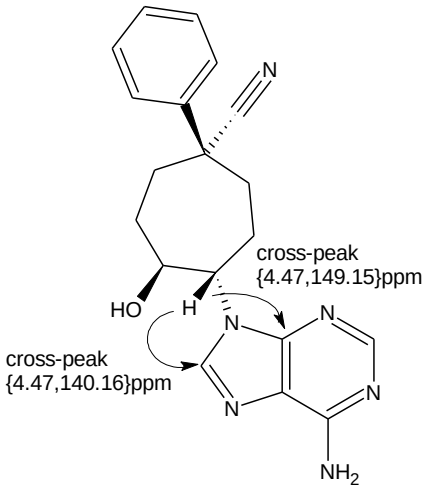
To a vigorously stirred solution of phenylacetonitrile (17.6 g, 150 mmol) in the dry DMF (120 ml) a suspension of NaH (12.9 g, 330 mmol) previously washed with hexane was added portionwise at -10$^o$C under inert atmosphere. The resulting suspension was stirred at -10$^o$C over 1 h. Then a solution of 1-bromobutene-4 (42.5 g, 315 mmol) in the dry DMF (60 ml) was added dropwise at -5$^o$C. The reaction mixture was warmed to a room temperature and allowed to stand overnight. The resulting mixture was diluted with saturated water solution of $NH_4Cl$ (800 ml) and extracted with MTBE (2x600 ml). Combined organic layers were washed with water (2x500 ml), separated and dried over $Na_2SO_4$. The solvent was evaporated under reduced pressure and a residue was purified by flash chromatography on silica gel (Eluent Hexane:DCM, 4:1) to give 27.0 g of a compound **3**.
Yield: 80%; pale yellow oil.

$^1$H NMR (400MHz, DMSO-$d_6$): δ – 1.75 (2H, m), 2.13 (6H, m), 4.63 (4H, dd, *J* = 12 Hz / 4Hz), 5.75 (2H, m), 7.38 (5H, m).
$[M+H]^+$ *m/z* – not detected.
Anal. $C_{16}H_{19}N$ (225): calc. C 85.29; H 8.50; N 6.22; found C 85.33; H 8.43; N 6.28.

**1-Phenyl-cyclohept-4-enecarbonitrile (1)**

A solution of compound **3** (22.5 g, 100 mmol) and 1$^{st}$ generation Grubbs' catalyst (0.2 g, 0.25 mmol) in dry DCM (800 ml) was refluxed over 3 h under inert atmosphere. Then the solvent was evaporated under reduced pressure and a residue was purified by flash chromatography on silica gel (Eluent Hexane:DCM, 1:1) to give 19.6 g of the compound **1**.
Yield: 99%; thick pale yellow oil.
$^1$H NMR (400MHz, DMSO-$d_6$): δ – 1.88 (2H, m), 2.13 (2H, m), 2.38 (2H, m), 2.63 (2H, m), 5.88 (2H, m), 7.25 (1H, m), 7.38 (2H, t, *J* = 8.5 Hz), 7.50 (2H, d, *J* = 8.5 Hz).
$[M+H]^+$ *m/z* – not detected.
Anal. $C_{14}H_{15}N$ (197): calc. C 85.24; H 7.66; N 7.10; found C 85.28; H 7.59; N 7.03.

The structure of compound **4a** was confirmed by the NMR $^1$H-$^{13}$C HMBC experiment as shown below.



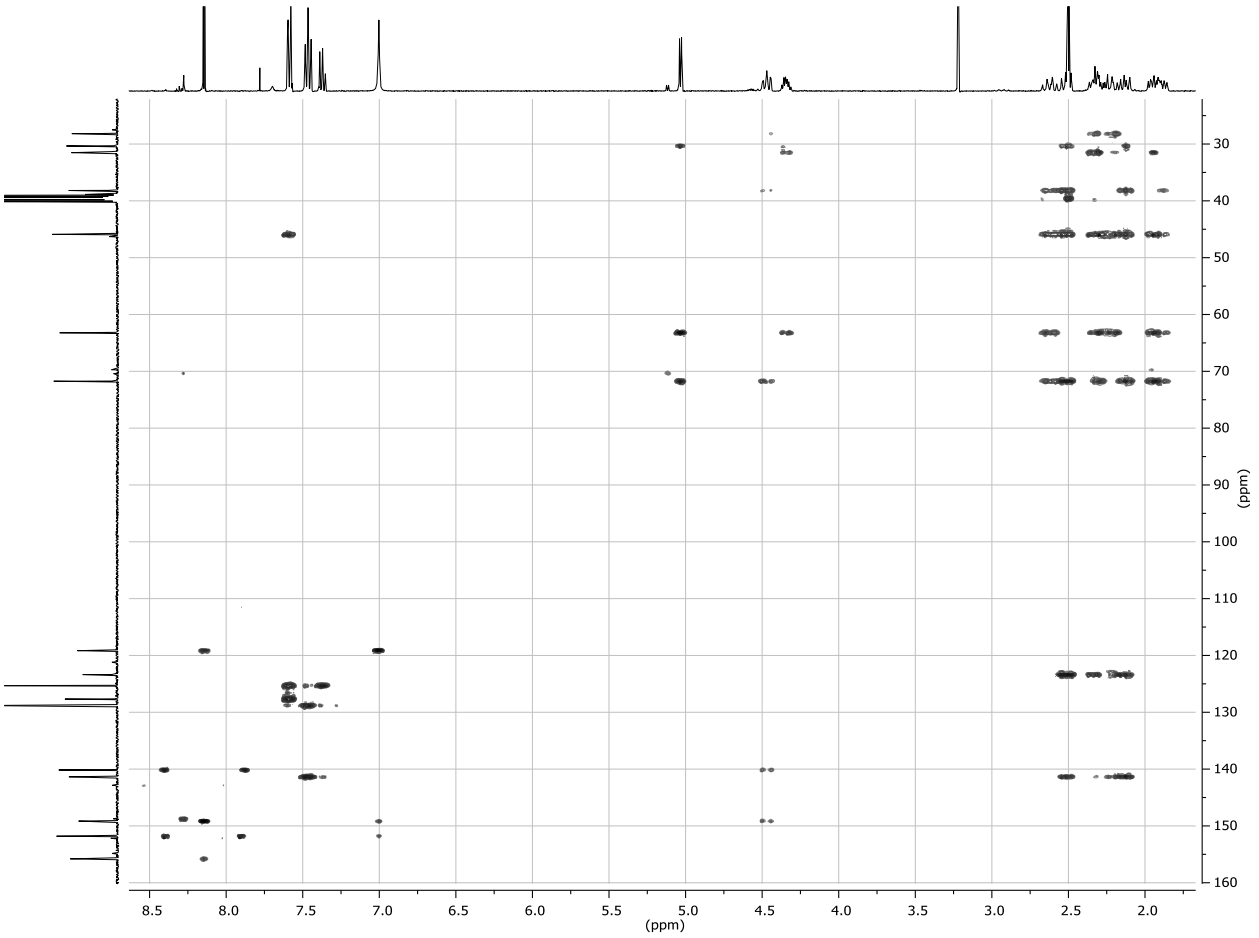
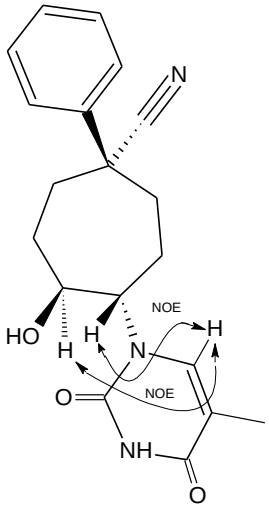



**Figure S1** $^{1}$H-$^{13}$C HMBC spectrum of (1*R*,4*S*,5*S*)-4-(6-amino-9*H*-purin-9-yl)-5-hydroxy-1-phenylcycloheptanecarbonitrile (**4a**).

The structure of compound **4b** was confirmed by $^{1}$H NMR 2D-NOESY experiment as shown below.



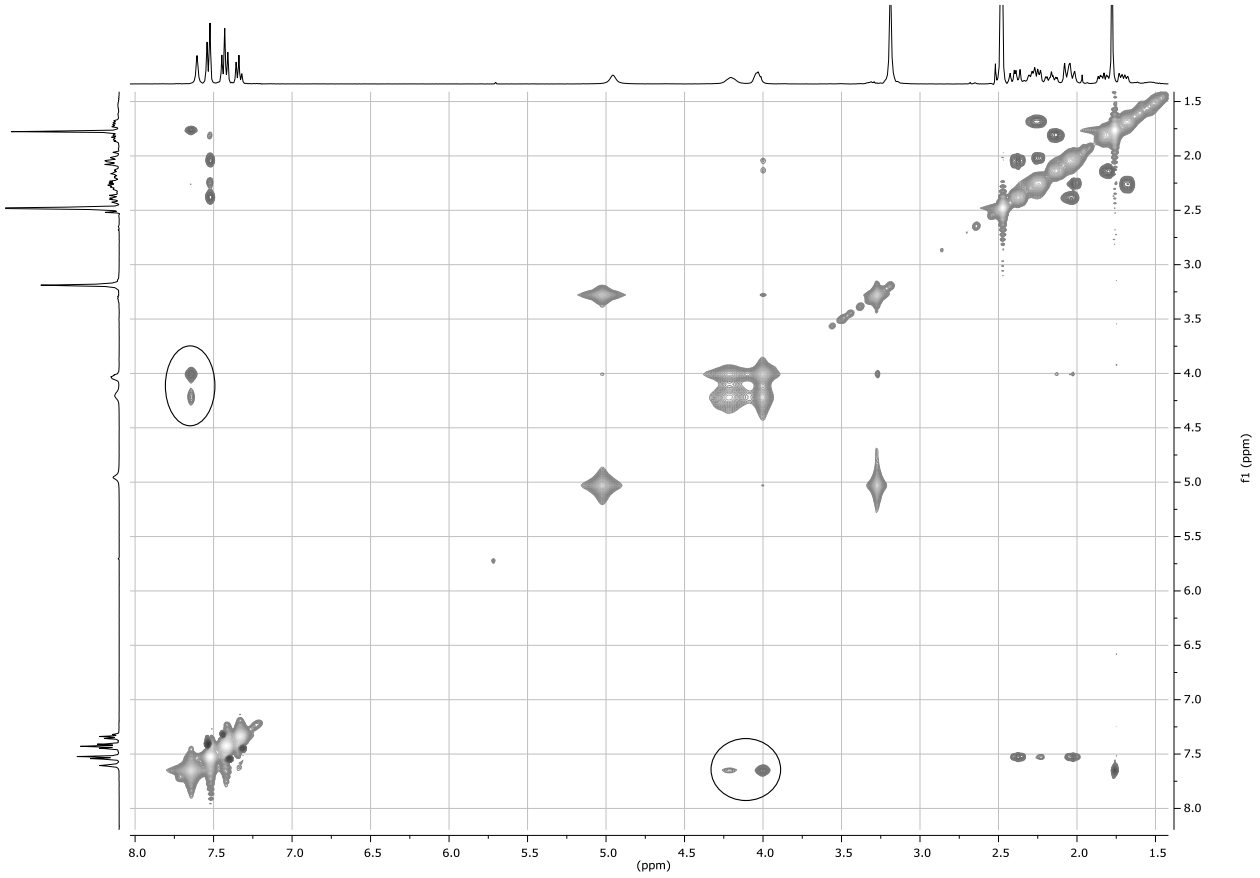



**Figure S2** 2D-NOESY spectrum of (1*R*,4*S*,5*S*)-4-hydroxy-5-(5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-1-phenylcycloheptanecarbonitrile (**4b**).