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trans-2-(Azaarylsulfanyl)cyclohexanol derivatives as potential pH-triggered conformational switches

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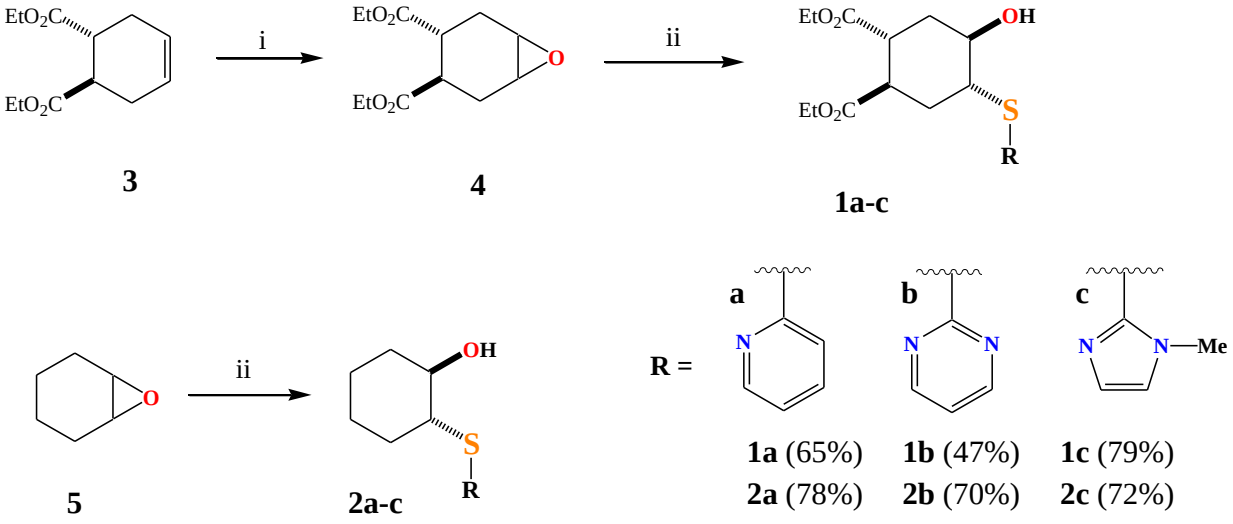
Experimental

The chemicals were commercial (Sigma-Aldrich, VWR, TCI) and were used as purchased. Conventional techniques were used to purify all solvents prior to use. Column chromatography was performed on silica gel (40-75 μm, Sorbent Technologies). The reactions were monitored by TLC on silica gel 2.5 × 7.5 cm plates, Analtech Inc (eluent hexane/EtOAc; visualization by UV and staining with I_2).

^{1}H NMR and ^{13}C NMR spectra were acquired on JEOL ECA-600 NMR spectrometer (600 MHz for ^{1}H and 150 MHz for ^{13}C) with spinning at room temperature. ^{1}H-^{1}H-COSY and ^{1}H-^{13}C-HMQC techniques were used to assign the signals. High-resolution mass spectra (HRMS) were obtained on a JEOL AccuTOF time-of-flight mass spectrometer (Peabody, MA) coupled with an Ionsense DART open-air ionization source (Saugus, MA).



Scheme S1 *Reagents and conditions:* i, *m*CPBA, CH_2Cl_2, 0 °C, 13 h; ii, RSH, $Na_2B_4O_7 \cdot 10H_2O$, THF, H_2O, room temperature, 48-72 h.

General procedure for the epoxide ring opening

Diethyl (3,4-*trans*)-7-oxabicyclo[4.1.0]heptane-3,4-dicarboxylate 4 was obtained from diethyl cyclohex-4-ene-1,2-dicarboxylate **3** as described previously [V. V. Samoshin, Y. Zheng and X. Liu, *J. Phys. Org. Chem.* 2017, **30** (11), e3689 (https://doi.org/ 3610.1002/poc.3689)].

Epoxide **4** or **5** (1.11 mmol) and sodium tetraborate (1.30 mmol) were dissolved in THF and/or H_2O (10 ml) at room temperature. The corresponding thiol (2-mercaptopyridine, 2-mercaptopyrimidine or 2-mercapto-1-methylimidazole, 1.70 mmol) was added under argon while stirring at room temperature (TLC monitoring until the consumption of epoxide). The mixture was diluted with H_2O (7 ml) and washed with CH_2Cl_2 (3x15 ml). The combined organic layer was dried for 12 h over anhydrous Na_2SO_4, the solvent was removed on rotary evaporator, and the crude product was purified by column chromatography.

Diethyl (1*r*,2*t*,4*c*,5*t*)-4-hydroxy-5-(pyridin-2-ylthio)cyclohexane-1,2-dicarboxylate 1a

The reaction was performed in H_2O (10 ml) for 72 h. The residue was purified as colourless oil by column chromatography (silica gel; hexane/EtOAc, 7:3) to give 293 mg (65%) of **1a**. R_f; 0.20 (hexane/EtOAc, 7:3). ^{1}H NMR (600 MHz, CD_3OD): δ 1.23 (t, *J* = 7.0 Hz, 3H; CH_3), 1.25 (t, *J* = 7.1 Hz, 3H; CH_3), 1.92 (m, 1H; H2ax), 2.02 (m, 2H; H2eq, H6eq), 2.35 (ddd, *J* = 13.8, 12.4, 4.1 Hz, 1H; H6ax), 2.90 (ddd, *J* = 12.0, 10.9, 3.8 Hz, 1H; H1), 3.07 (ddd, *J* = 12.0, 10.8, 4.1 Hz, 1H; H2), 4.03 (q, *J* = 3.5 Hz, H4), 4.13 (m, 4H; OCH_2), 4.19 (q, *J* = 3.5 Hz, 1H; H5), 7.11 (m , 1H; pyridinyl), 7.30 (m , 1H; pyridinyl), 7.62 (td , J = 8.0, 2.0 Hz, 1H; pyridinyl), 8.41 (m , 1H; pyridinyl). ^{13}C NMR (150 MHz, CD_3OD): δ 13.12 ($2CH_3$, Et), 28.11 (C6), 31.15 (C3), 39.09 (C2), 40.84 (C1), 44.14 (C5), 60.50, 60.55 (OCH_2), 67.42 (C4), 120.06, 122.76, 136.64, 146.27 (CH, pyridinyl), 157.45 (C, pyridinyl), 174.41, 174.52 (C=O). HMRS: *m/z* 354.1377 $[M+H]^+$. Calculated for $C_{17}H_{24}NO_5S^+$, *m/z* 354.1370.

Diethyl (1*r*,2*t*,4*c*,5*t*)-4-hydroxy-5-(pyrimidin-2-ylthio)-cyclohexane-1,2-dicarboxylate 1b

The reaction was performed in 1:1 H_2O/THF mixture (10 ml) for 72 h. The residue was purified as yellow oil by column chromatography (silica gel; hexane/EtOAc, 7:3) to give 0.184 mg (47%) of **1b**. R_f; 0.13 (hexane/EtOAc, 7:3). ^{1}H NMR (600 MHz, CD_3OD): δ 1.23 (t, *J* = 7.1 Hz, 3H; CH_3), 1.25 (t, *J* = 7.0 Hz, 3H; CH_3), 1.88 (m, 1H; H2ax), 2.04 (dtd, *J* = 14.1, 4.0, 1.5 Hz, 1H; H3eq), 2.10 (dt, *J* = 13.9, 3.5 Hz, H6eq), 2.37 (ddd, *J* = 13.6, 12.8, 4.2 Hz, 1H; H6ax), 2.86

(ddd, *J* = 12.3, 11.0, 3.8 Hz, 1H; H1), 3.08 (ddd, *J* = 12.1, 11.1, 4.0 Hz, 1H; H2), 4.10 (q, *J* = 3.7 Hz, 1H; H4), 4.13 (m, 4H; OCH2), 4.22 (q, *J* = 3.6 Hz, 1H; H5), 7.16 (t , *J* = 4.9 Hz, 1H; pyrimidinyl), 8.58 (d , *J* = 4.9 Hz, 2H; pyrimidinyl). ^{13}C NMR (150 MHz, CD3OD): δ 13.10 (2CH_3, Et), 27.89 (C6), 31.23 (C3), 39.03 (C1), 40.96 (C2), 44.60 (C5), 60.50, 60.58 (OCH2), 67.07 (C4), 117.13 (CH; pyrimidinyl), 157.65 (2C, CH; pyrimidinyl), 170.61 (C; primidinyl) 174.53 (C=O), 175.09 (C=O). HRMS: m/z 355.1334 $[M+H]^+$. Calculated for $C_{16}H_{23}N_2O_5S^+$, m/z 355.1322.

Diethyl (1*r*,2*t*,4*c*,5*t*)-4-hydroxy-5-[(1-methyl-1*H*-imidazol-2-yl)thio]cyclohexane-1,2-dicarboxylate 1c

The reaction was performed in H_2O (10 ml) for 48 h. The residue was purified as colourless oil by column chromatography (silica gel; hexane/EtOAc, 1:4) to give 481 mg (79%) of **1c**. R_f; 0.23 (hexane/EtOAc, 1:4). ^{1}H NMR (600 MHz, CD_3OD): δ 1.23 (t, *J* = 7.1 Hz, 3H; CH_3), 1.25 (t, *J* = 7.0 Hz, 3H; CH_3), 1.88 (dt, *J* = 14.1, 3.9 Hz, 1 1H; H6eq), 1.94 (dt, *J* = 14.0, 4.0 Hz, 1H; H3eq), 2.06 (m, 1H; H3ax), 2.22 (ddd, *J* = 14.1, 11.3, 4.0 Hz, 1H; H6ax), 2.99 (ddd, *J* = 11.1, 10.1, 3.8 Hz, 1H; H2), 3.05 (td, *J* = 11.1, 4.0 Hz, 1H; H1), 3.45 (q, *J* = 4.0 Hz, 1H; H5), 3.77 (s, 3H; CH_3-imidazolyl), 3.88 (q, *J* = 3.8 Hz, 1H; H4), 4.13 (m, 4H; OCH_2), 7.04 (d, *J* = 1.4 Hz, 1H; H; imidazolyl), 7.24 (d, *J* = 1.4 Hz, 1H; H; imidazolyl). ^{13}C NMR (150 MHz, CD3OD): δ 13.11, 13.12 (2CH_3, Et), 28.02 (C6), 30.64 (C3), 32.90 (CH_3; imidazolyl) 39.30 (C2), 40.12 (C1), 49.99 (C5), 60.55, 60.61 (OCH2), 66.98 (C4), 123.76, 128.56 (2C, CH; imidazolyl), 139.08 (C; imidazolyl) 174.19, 174.77 (C=O). HRMS: 357.1492 $[M+H]^+$. Calculated for $C_{16}H_{25}N_2O_5S^+$, m/z 357.1479.

***trans*-2-(Pyridin-2-ylthio)cyclohexan-1-ol 2a**

The reaction was performed in H_2O (10 ml) for 72 h. The residue was purified as yellow oil by column chromatography (silica gel; CH_2Cl_2/EtOAc, 9:1) to give 0.180 mg (78%) of **2a**. R_f; 0.27 (CH_2Cl_2/EtOAc, 9:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.33 (m, 3H; H3, H4, H5), 1.49 (m, 1H; H6ax), 1.77 (m, 2H; H4, H5), 2.14 (m, 1H; H6eq), 2.22 (m, 1H; H3eq), 3.42 (ddd, *J* = 12.8, 9.9, 4.0 Hz, 1H; H1), 3.51 (td, J = 10.1, 4.3 Hz, 1H; H2), 6.13 (s, 1H; OH), 7.03 (ddd, *J* = 7.3, 5.1, 1.1 Hz, 1H; H; pyridinyl), 7.29 (dt, *J* = 8.1, 1.0 Hz, 1H; H; pyridinyl), 7.51 (ddd, *J* = 7.9, 7.5, 1.9 Hz, 1H; H; pyridinyl), 8.35 (m, 1H; H; pyridinyl). ^{13}C NMR (150 MHz, $CDCl_3$): δ 24.26

(C5), 26.38 (C4), 32.50 (C6), 36.28 (C3), 52.41 (C1), 76.09 (C6), 120.16, 123.44, 136.66, 148.76 (CH; pyridinyl), 159.62 (C; pyridinyl). HRMS: m/z 210.0954 $[M+H]^+$. Calculated for $C_{11}H_{16}NOS^+$, m/z 210.0947.

***trans*-2-(Pyrimidin-2-yl-hio)cyclohexan-1-ol 2b**

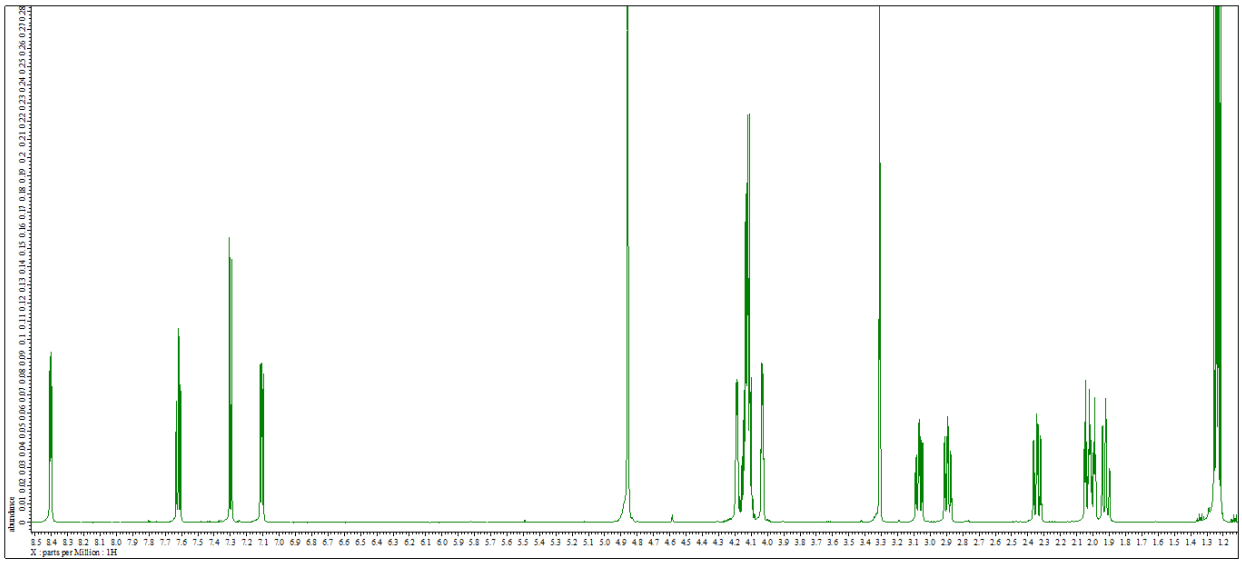
The reaction was performed in H_2O (10 ml) for 72 h. The residue was purified as colourless oil by column chromatography (silica gel; hexane/EtOAc, 1:1) to give 0.162 mg (70%) of **2b**. R_f; 0.21 (hexane/EtOAc, 1:1). ^{1}H NMR (600 MHz, CD_3OD): δ 1.47 (m, 4H; H3, H4, H5, H6), 1.68 (m, 1H; H4ax), 1.78 (m, 1H; H5ax), 2.08 (m, 1H; H6ax), 2.27 (m, 1H; H3ax), 3.57 (td, *J* = 9.4, 4.0 Hz, 1H; H1), 3.77 (ddd, *J* = 10.6, 9.5, 4.1 Hz, 1H; H2), 7.11 (t, *J* = 4.9 Hz, 1H, H; pyrimidinyl), 8.54 (d, *J* = 4.9 Hz, 2H, H; pyrimidinyl).^{13}C NMR (150 MHz, CD_3OD): δ 23.64 (C5), 25.17 (C4), 31.72 (C3), 34.64 (C6), 50.51 (C2) 71.58 (C1), 116.63 (CH; pyrimidinly), 157.31 (2C, CH; pyrimidinly), 172.36 (C; pyrimidinyl). HRMS: m/z 211.0915 $[M+H]^+$. Calculated for $C_{10}H_{15}N_2OS^+$, m/z 211.0900.

***trans*-2-[(1-methyl-1*H*-imidazol-2-yl)thio]cyclohexan-1-ol 2c**

The reaction was performed in H_2O (10 ml) for 48 h. The residue was purified as colorless oil by column chromatography (silica gel; EtOAc) to give 0.168 mg (72%) of **2c**. R_f; 0.34 (EtOAc). ^{1}H NMR (600 MHz, CD_3OD): δ 1.30 (m, 4H; H3, H4, H5, H6), 1.64 (m, 1H; H4), 1.72 (m, 1H; H5), 1.94 (m, 1H; H3), 2.02 (m, 1H; H6), 2.94 (ddd, *J* = 11.1, 9.5, 4.0 Hz, 1H; H2), 3.39 (td, J = 9.7, 4.2 Hz, 1H; H1), 3.75 (s, 3H; CH_3-imidazolyl), 7.02 (d, *J* = 1.3 Hz, 1H; H; imidazolyl), 7.21 (d, *J* = 1.3 Hz, 1H; H; imidazolyl). ^{13}C NMR (150 MHz, CD_3OD): δ 23.90 (C5), 25.30 (C4), 32.26 (C3), 33.02 (CH_3; imidazolyl), 34.82 (C6), 55.41 (C2), 72.78 (C1), 123.46, 128.13 (CH; imidazolyl), 139.72 (C; imidazolyl). HRMS: m/z 213.1063 $[M+H]^+$. Calculated for $C_{10}H_{17}N_2OS^+$, m/z 213.1056.

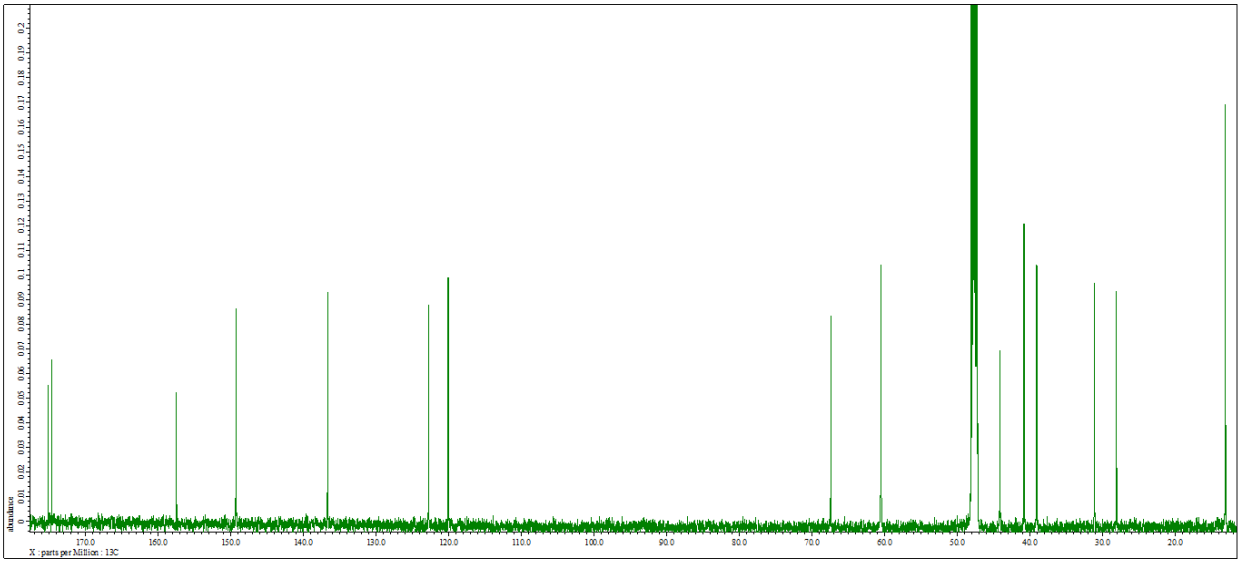
Diethyl (1*r*,2*t*,4*c*,5*t*)-4-hydroxy-5-(pyridin-2-ylthio)cyclohexane-1,2-dicarboxylate 1a

(^{1}H NMR, 600 MHz, CD_3OD)



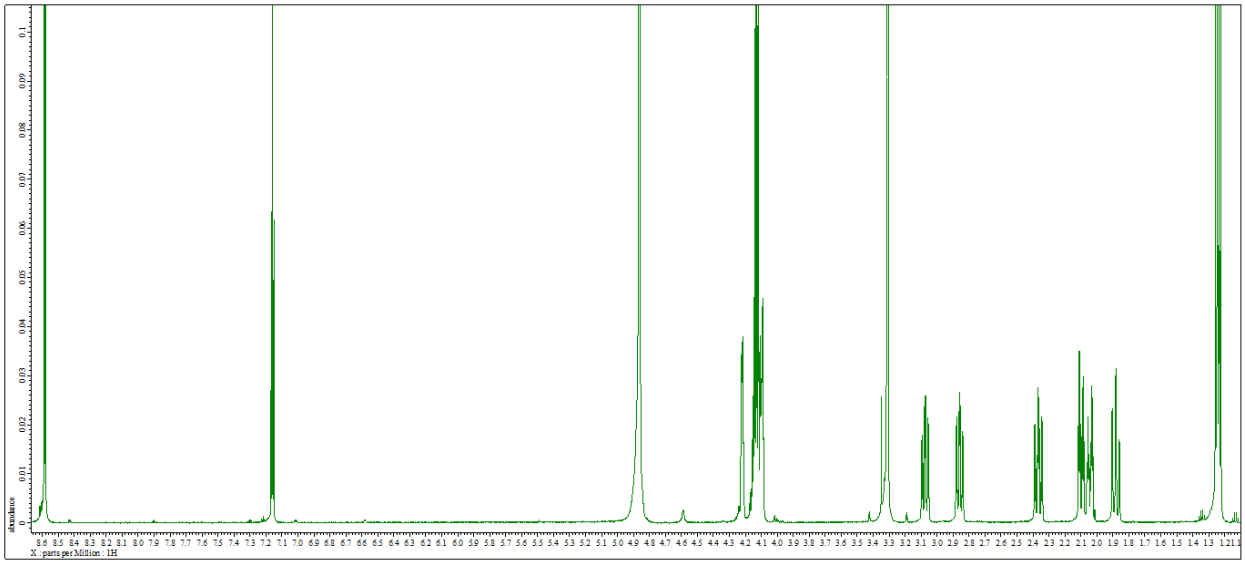
Diethyl (1*r*,2*t*,4*c*,5*t*)-4-hydroxy-5-(pyridin-2-ylthio)cyclohexane-1,2-dicarboxylate 1a

(^{13}C NMR, 150 MHz, CD_3OD)



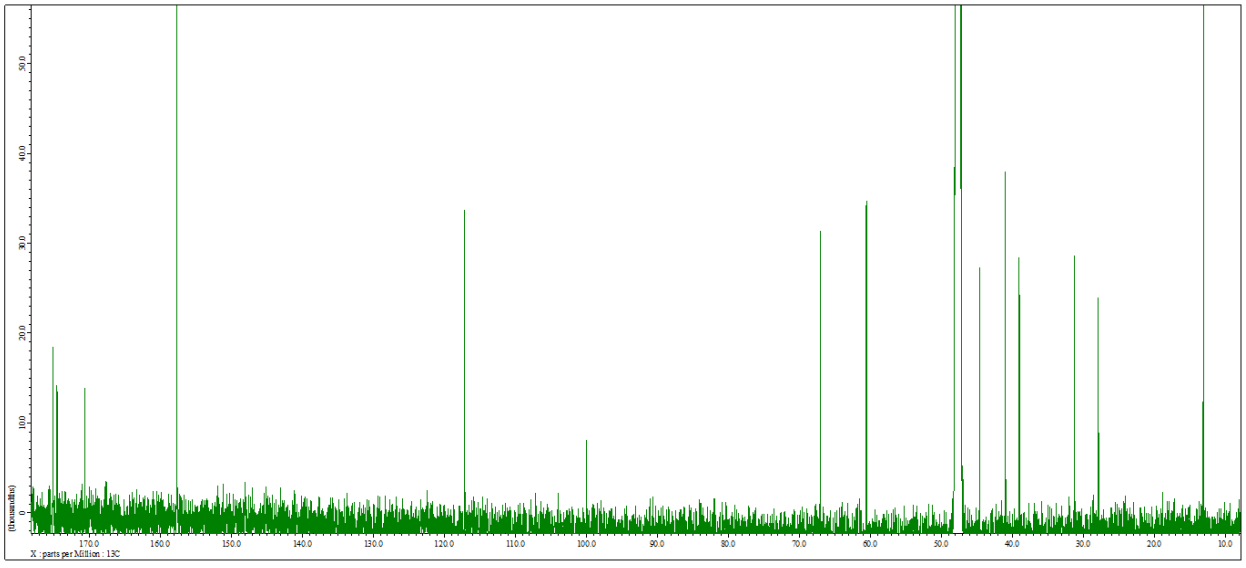
Diethyl (1*r*,2*t*,4*c*,5*t*)-4-hydroxy-5-(pyrimidin-2-ylthio)-cyclohexane-1,2-dicarboxylate 1b

(^{1}H NMR, 600 MHz, CD_3OD)

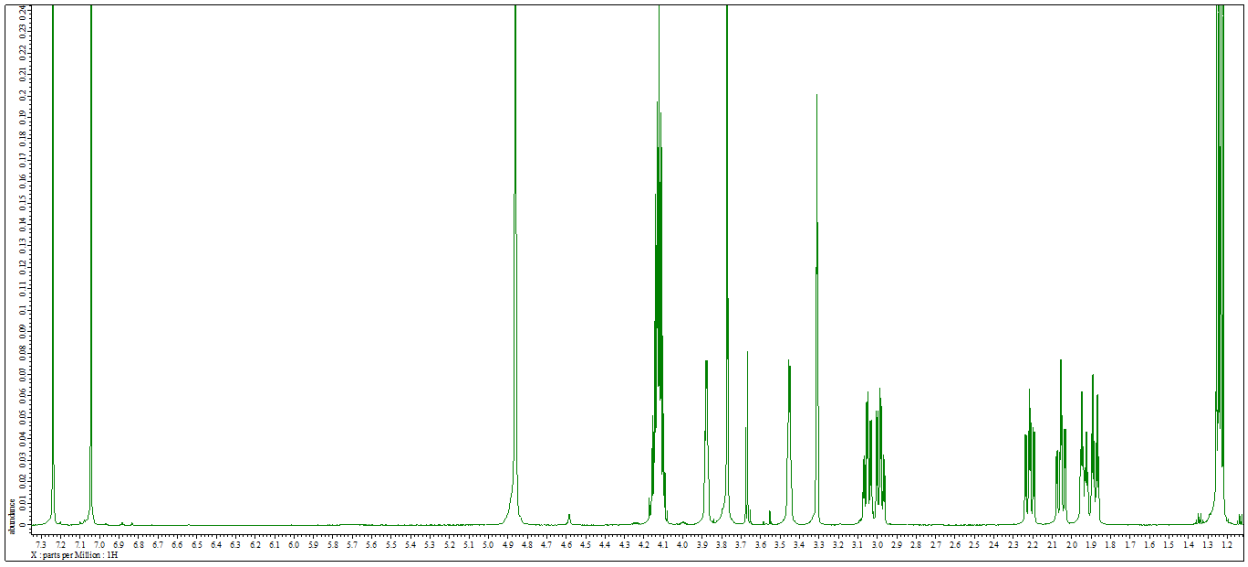


Diethyl (1*r*,2*t*,4*c*,5*t*)-4-hydroxy-5-(pyrimidin-2-ylthio)-cyclohexane-1,2-dicarboxylate 1b

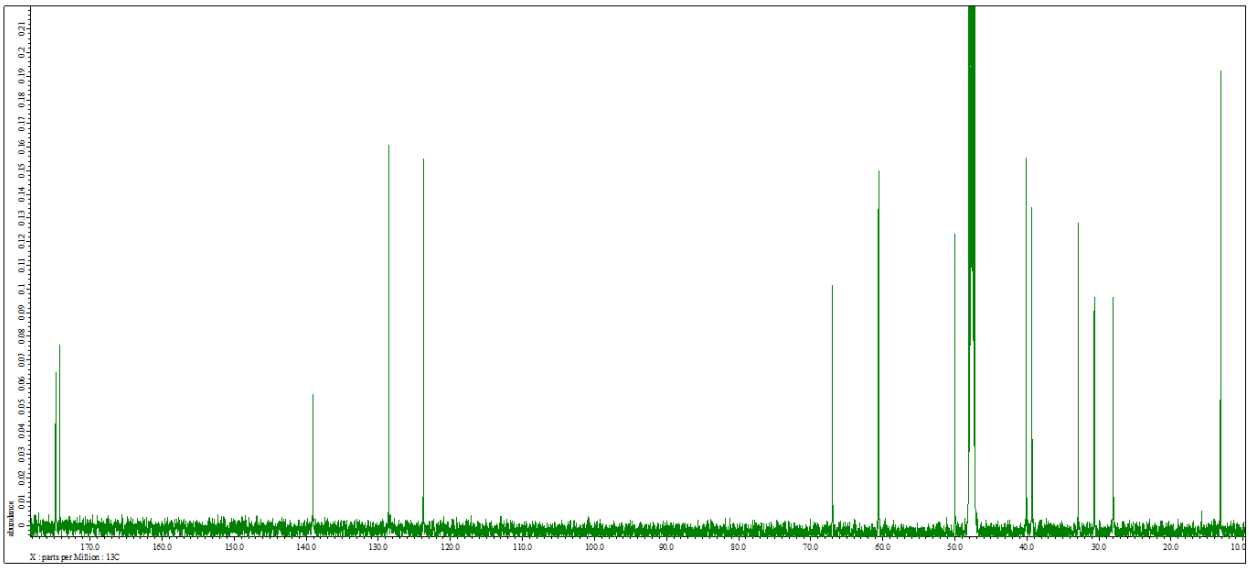
(^{13}C NMR, 150 MHz, CD_3OD)



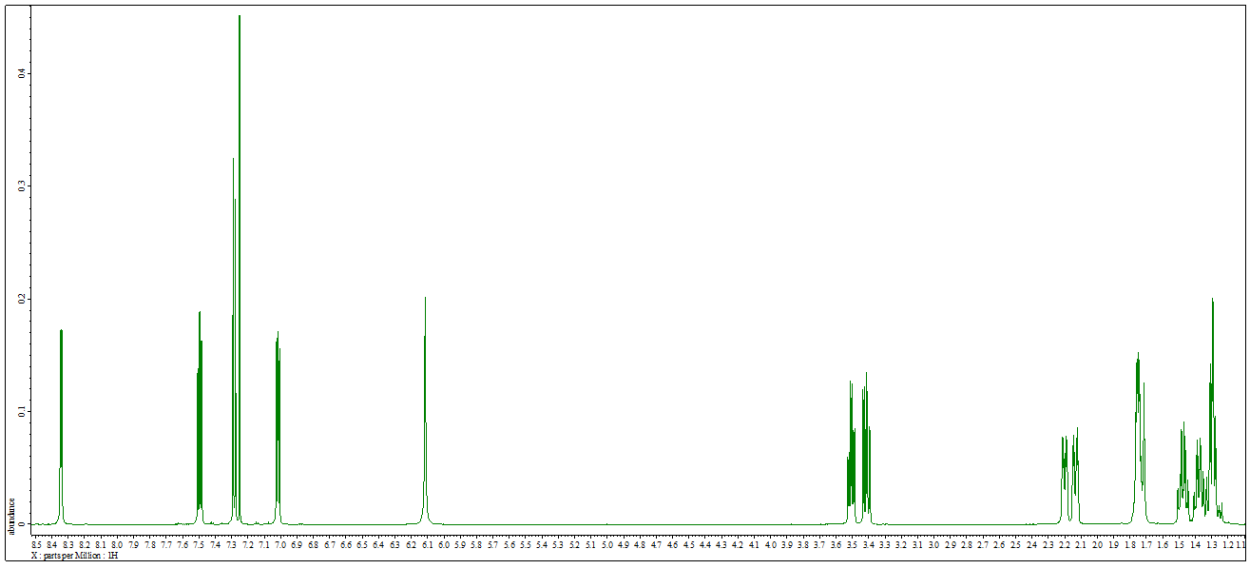
Diethyl (1*r*,2*t*,4*c*,5*t*)-4-hydroxy-5-[(1-methyl-1*H*-imidazol-2-yl)thio]cyclohexane-1,2-dicarboxylate 1c (^{1}H NMR, 600 MHz, CD_3OD)



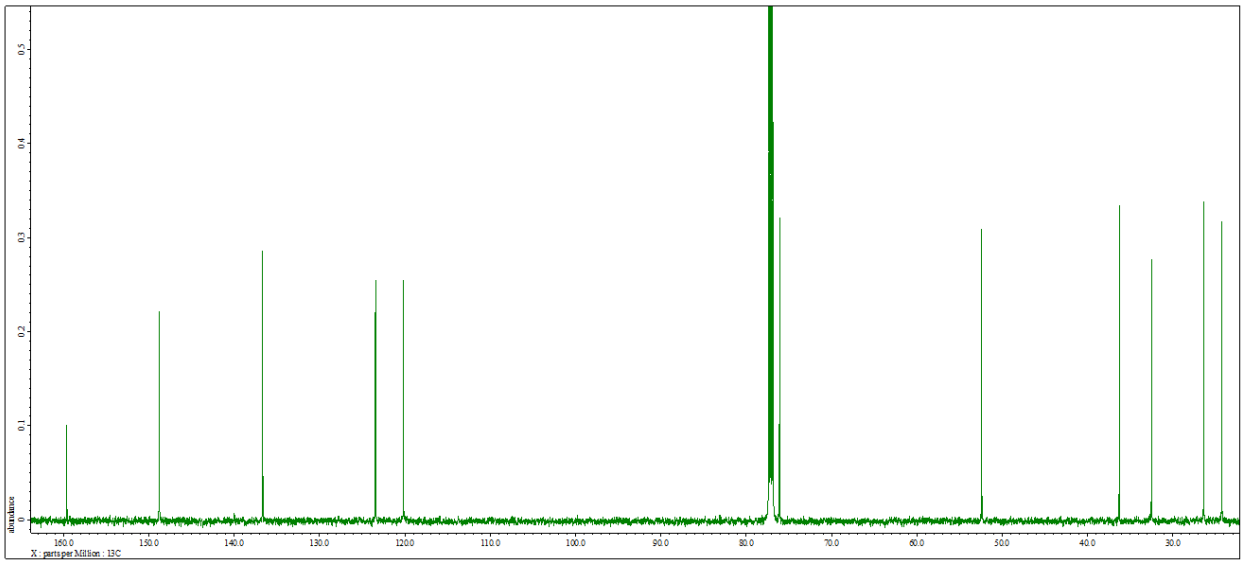
Diethyl (1*r*,2*t*,4*c*,5*t*)-4-hydroxy-5-[(1-methyl-1*H*-imidazol-2-yl)thio]cyclohexane-1,2-dicarboxylate 1c (^{13}C NMR, 150 MHz, CD_3OD)



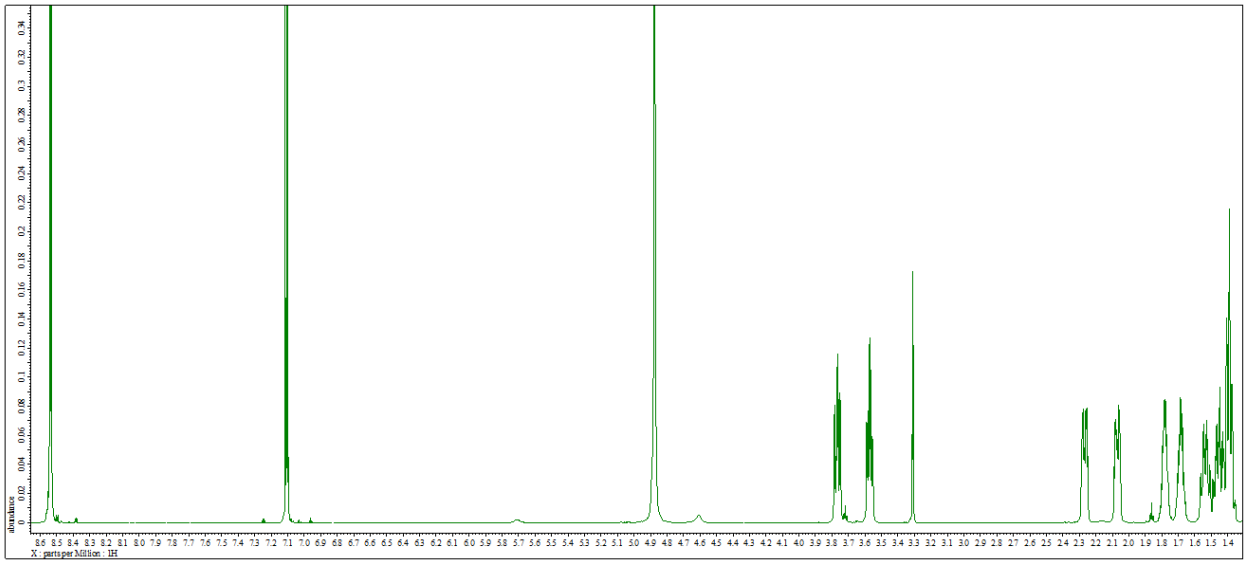
***trans*-2-(Pyridin-2-ylthio)cyclohexan-1-ol 2a (^{1}H NMR, 600 MHz, $CDCl_3$)**



***trans*-2-(Pyridin-2-ylthio)cyclohexan-1-ol 2a (^{13}C NMR, 150 MHz, $CDCl_3$)**



***trans*-2-(Pyrimidin-2-yl-hio)cyclohexan-1-ol 2b (^{1}H NMR, 600 MHz, CD_3OD)**



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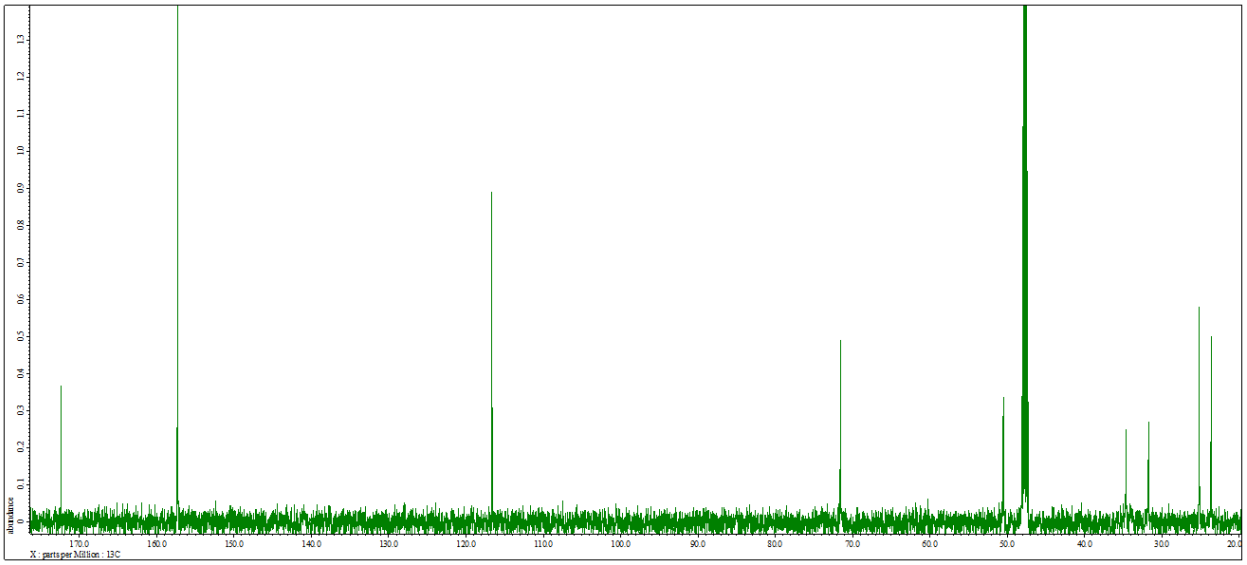
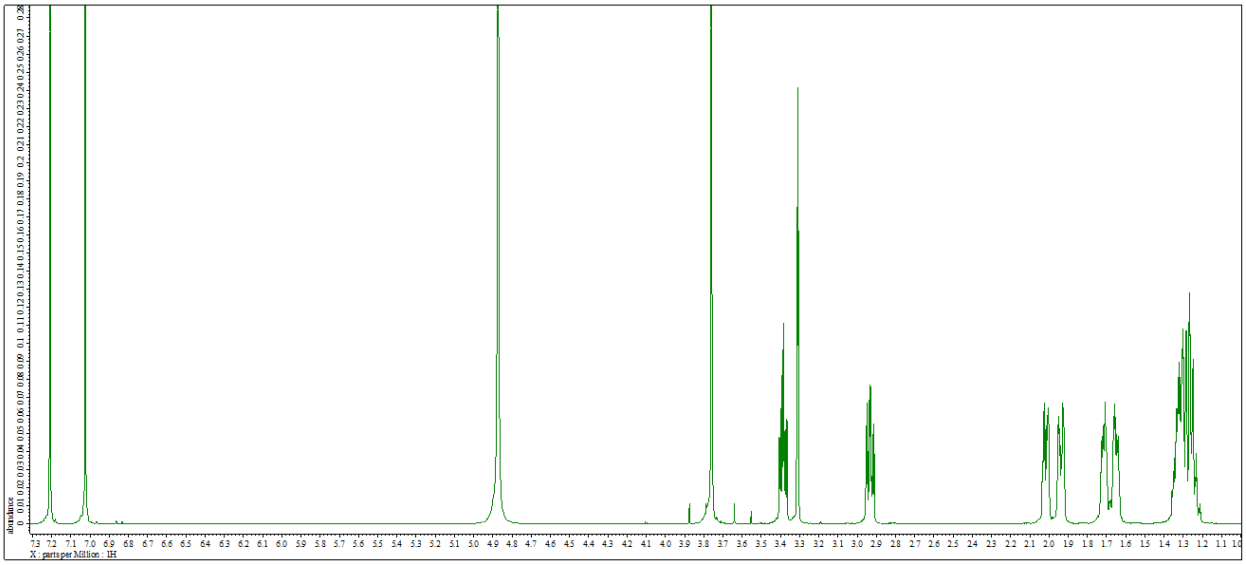


***trans*-2-[(1-methyl-1*H*-imidazol-2-yl)thio]cyclohexan-1-ol 2c (^{1}H NMR, 600 MHz, CD_3OD)**



***trans*-2-[(1-methyl-1*H*-imidazol-2-yl)thio]cyclohexan-1-ol 2c (^{13}C NMR, 150 MHz, CD_3OD)**