

Supporting Information

for

Biocatalytic Hydrogen-Transfer To Access Enantiomerically Pure Proxiphylline, Xanthinol, and Diprophylline

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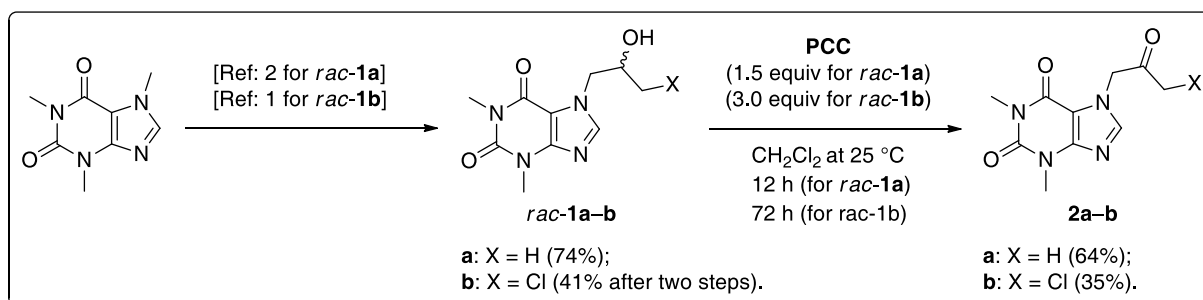
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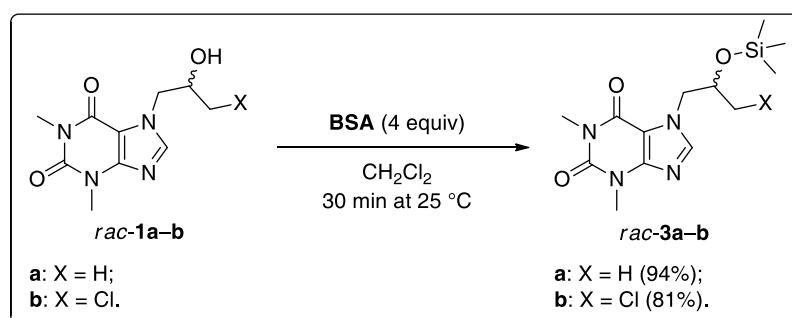
1. Synthesis of the Prochiral Starting Materials 2a–b



Prior to developing the bioreduction step, the syntheses of both racemic alcohols *rac-1a–b* and the corresponding ketones **2a–b** were performed following the methods already reported in the literature. Firstly, to obtain racemic proxyphylline (*rac-1a*), the triethylamine-mediated regioselective ring-opening of racemic propylene oxide with commercially available theophylline in methanol was performed furnishing the product in 74% yield [1]. In turn, the synthesis of racemic 7-(3-chloro-2-hydroxypropyl)theophylline (*rac-1b*) was accomplished in a 2-step reaction sequence by the K₂CO₃-mediated regioselective ring-opening of racemic epichlorohydrin with theophylline dissolved in dimethylformamide, followed by the treatment of the obtained epoxide with 36% HCl in chloroform [2]. In this case, the desired chlorohydrin *rac-1b* was synthesized in 41% total yield after two steps.

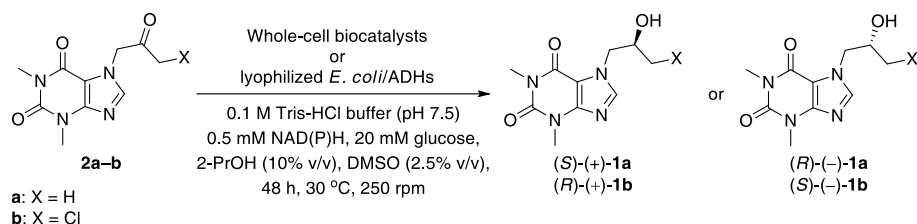
The resulting alcohols *rac-1a–b* were then chemically oxidized using a suspension of pyridinium chlorochromate (PCC) in dichloromethane, thus furnishing prochiral ketones: **2a** in 64% yield and **2b** in 33% yield, respectively. In the case of PCC-mediated oxidation of *rac-1a*, the oxidizing agent was used in 1.5 equiv, and the reaction was stopped after 12 h. In contrast, the oxidation of *rac-1b* required 3 equiv of PCC and additional elongation of the reaction time up to 72 h to reach only half of the yield achieved for **2a**.

2. Synthesis of the Silylated Derivatives *rac-3a–b* for GC analysis



Subsequently, GC analytical methods to separate the corresponding alcohol-ketone pair requested for reliable measurement of the enzymatic reaction conversion values (% conv.) have been undertaken. However, it turned out that the baseline resolution for the alcohol-ketone mixtures using a semi-polar GC-column could not be reached in both cases. Therefore, silylation of the polar hydroxyl groups in alcohols *rac-1a–b* using standard derivatization protocol employing *N,O*-bis(trimethylsilyl)acetamide (BSA) in dichloromethane had to be applied to obtain more volatile compounds characterized by much lower values of the retention times (*t_R*) than ketones. As we needed trimethylsilyl ethers *rac-3a–b* in more significant amounts to proceed with calibration curves for GC analyses, the preparative scale for the silylation reaction was also performed, furnishing both derivatives in the range of 81–94% yield (after column chromatography), respectively.

Table S1. Analytical-scale studies on stereoselective reduction of ketones **2a–b** (10 mM final conc.) with different biocatalysts.



| Entry | Biocatalyst/Cofactor ^a | 2a | | 2b | |
|-------|---|------------------------|---|------------------------|---|
| | | Conv. ^b [%] | ee _p ^c [%] (Config. ^d) | Conv. ^b [%] | ee _p ^c [%] (Config. ^d) |
| 1 | <i>Pichia pastoris</i> ATCC 76273/NADH | N.D. ^e | N.A. ^f | N.D. ^e | N.A. ^f |
| 2 | <i>Pseudomonas</i> sp. DSM 6978 / NADH | N.D. ^e | N.A. ^f | N.D. ^e | N.A. ^f |
| 3 | <i>Arthrobacter</i> sp. DSM 7325/NADH | N.D. ^e | N.A. ^f | >99 ^g | 98 (S) |
| 4 | <i>Actinomyces</i> sp. SRB-AN040 FCC025/NADH | 30 | 99 (S) | >99 ^g | 80 (R) |
| 5 | <i>Actinomyces</i> sp. SRB-AN053 FCC027/NADH | N.D. ^e | N.A. ^f | N.D. ^e | N.A. ^f |
| 6 | <i>Actinomyces</i> sp. ARG-AN024 FCC014/NADH | N.D. ^e | N.A. ^f | 23 ^g | 85 (S) |
| 7 | ARG-AN025 FCC015/NADH | N.D. ^e | N.A. ^f | 9 ^g | 76 (S) |
| 8 | USA-AN012 FCC021/NADH | N.D. ^e | N.A. ^f | 16 ^g | 59 (S) |
| 9 | <i>E. coli</i> /TeSADH/NADH ^h | N.D. ^e | N.A. ^f | N.D. ^e | N.A. ^f |
| 10 | <i>E. coli</i> /TeSADH/NADPH ^h | - | - | >99 | 36 (S) |
| 11 | <i>E. coli</i> /ADH-T/NADH ^h | N.D. ^e | N.A. ^f | N.D. ^e | N.A. ^f |
| 12 | <i>E. coli</i> /ADH-T/NADPH ^h | - | - | N.D. ^e | N.A. ^{f,g} |
| 13 | <i>E. coli</i> /ReADH/NADH ^h | N.D. ^e | N.A. ^f | N.D. ^e | N.A. ^f |
| 14 | <i>E. coli</i> /ReADH/NADPH ^h | - | - | N.D. ^e | N.A. ^{f,g} |
| 15 | <i>E. coli</i> /RasADH/NADH ^h | 18 | 60 (S) | >99 | 12 (R) |
| 16 | <i>E. coli</i> /RasADH/NADPH ^h | - | - | >99 | 20 (R) |
| 17 | <i>E. coli</i> /SyADH/NADH ^h | N.D. ^e | N.A. ^f | N.D. ^e | N.A. ^{f,g} |
| 18 | <i>E. coli</i> /SyADH/NADPH ^h | - | - | >99 | 94 (R) |
| 19 | <i>E. coli</i> /ADH-A/NADH ^h | >99 | >99 (S) | N.D. ^e | N.A. ^{f,g} |
| 20 | <i>E. coli</i> /LB-ADH/NADH ^h | N.D. ^e | N.A. ^f | N.D. ^e | N.A. ^{f,g} |
| 21 | <i>E. coli</i> /LB-ADH/NADPH ^h | - | - | >99 | 61 (S) |
| 22 | <i>E. coli</i> /Lk-ADH-Lica/NADH ^h | >99 | >99 (R) | >99 | 99 (S) |
| 23 | <i>E. coli</i> /Lk-ADH/NADH ^h | N.D. ^e | N.A. ^f | N.D. ^e | N.A. ^{f,g} |
| 24 | <i>E. coli</i> /Lk-ADH/NADPH ^h | - | - | >99 | 61 (S) |
| 25 | <i>E. coli</i> /Lk-ADH Prince/NADH ^h | 88 | >99 (R) | >99 | 98 (S) |

^a Reaction conditions: lyophilized biocatalyst (10 mg), 20 mM glucose (in the case of wild-type microorganisms), 0.5 mM NAD(P)H, 0.1 M Tris-HCl buffer (pH 7.5)/2-PrOH (500 μ L, 90:10, v/v), DMSO (2.5% v/v), 48 h, 30 $^\circ$ C, 250 rpm (laboratory shaker).

^b Conversion values (%) (i.e., consumption of substrates **2a–b**) were determined by GC analyses after derivatization of crude mixture with BSA as a silylating reagent.

^c Determined for *non-rac-1a–b* by HPLC analyses using a Chiralcel AD-H column with a chiral stationary phase.

^d Absolute configuration of optically active products (*non-rac-1a–b*) established by comparing HPLC picks elution order with enantiomeric standards. Major enantiomer is shown in parentheses.

^e Not detected.

^f Not applicable because of no detectable conversion.

^g Complex mixture of byproducts.

^h Reaction conducted without glucose.

Table S2. Analytical separation conditions of studied compounds by GC column.

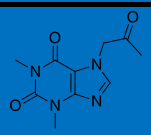
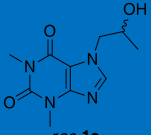
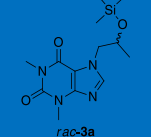
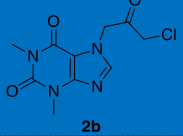
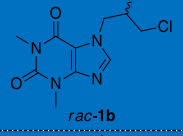
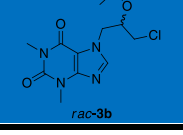
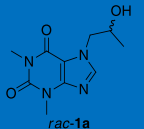
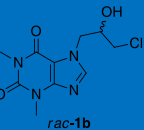
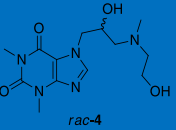
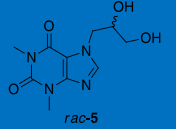
| Compound | Temperature program [°C] | Retention time [min] |
|---|--------------------------|----------------------|
|  2a | 260 (isothermal) | 3.95 |
|  rac-1a | | 4.01 |
|  rac-3a | | 2.64 |
|  2b | 260 (isothermal) | 6.41 |
|  rac-1b | | 6.56 |
|  rac-3b | | 4.39 |

Table S3. HPLC analytical separation conditions of purine derivatives by chiral columns – Chiralpak AD-H (Daicel®) or Lux i-Cellulose-5 (Phenomenex®).^[a]

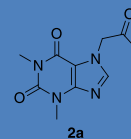
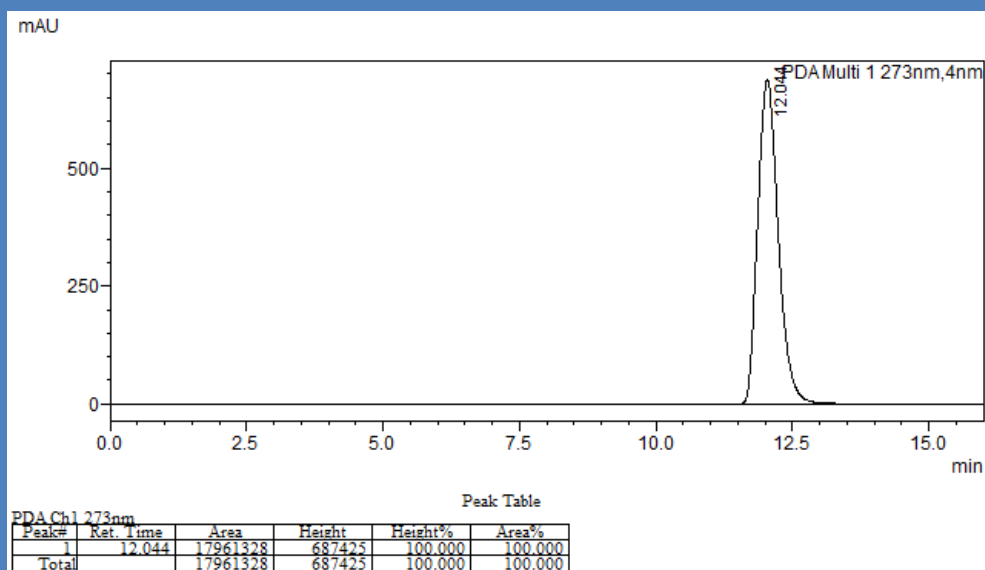
| Compound | HPLC Column | Mobile Phase | Flow Rate [mL/min] / Pressure [MPa] | Detection [nm] / Temperature [°C] | Retention Time [min] |
|--|-------------------|---|--|--|---|
| | | <i>n</i> -Hexane/IPA/DEA [v/v/v] ^[b] | | | |
|  <i>rac</i> -1a | Chiralpak AD-H | 78:22:0 ^[b] | 1.0 / 4.7 | 273 / 25 | 7.384 (<i>S</i>) and 8.541 (<i>R</i>) |
|  <i>rac</i> -1b | Chiralpak AD-H | 78:22:0 ^[b] | 0.3 / 1.6 | 273 / 25 | 33.585 (<i>R</i>) and 35.954 (<i>S</i>) |
| | Chiralpak AD-H | 78:22:0 ^[b] | 0.3 / 1.6 | 273 / 25 | 35.903 (<i>R</i>) and 39.419 (<i>S</i>) |
| Compound | HPLC Column | Mobile Phase | Flow Rate [mL/min] | Detection [nm] | Retention Time [min] |
| | | <i>n</i> -Hexane/EtOH/DEA [v/v/v] ^[b] | | | |
|  <i>rac</i> -4 | Lux i-Cellulose-5 | 70:30:0.1 | 1.0 / 7.4 | 273 / 25 | 24.449 (<i>S</i>) and 27.028 (<i>R</i>) |
|  <i>rac</i> -5 | Lux i-Cellulose-5 | 70:30:0 | 1.0 / 7.2 | 274 / 30 | 17.165 (<i>R</i>) and 19.342 (<i>S</i>) |

^[a] Performed on a Shimadzu Nexera-*i* (LC-2040C 3D) equipped with a photodiode array detector (PAD).

^[b] IPA states for 2-PrOH (propan-2-ol); EtOH states for ethanol; DEA states for diethylamine.

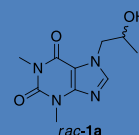
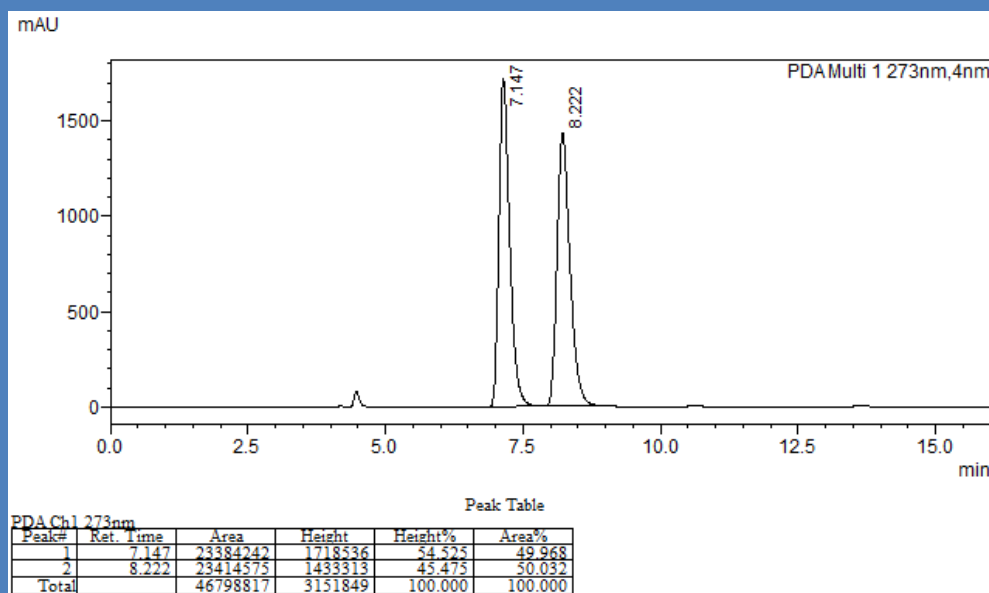
HPLC of 2a on Chiralpak AD-H at 25 °C

HPLC conditions: *n*-hexane-2-PrOH (78:22, v/v); *f*=1.0 mL/min; λ =273 nm; *p*=5.7 MPa



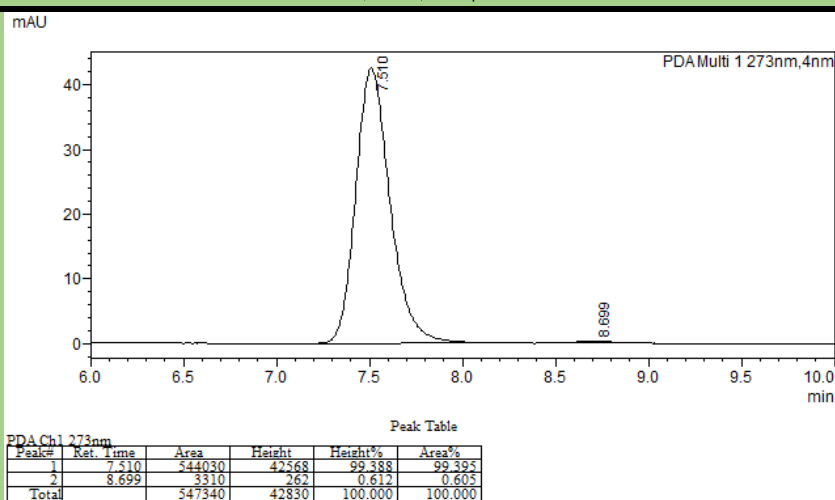
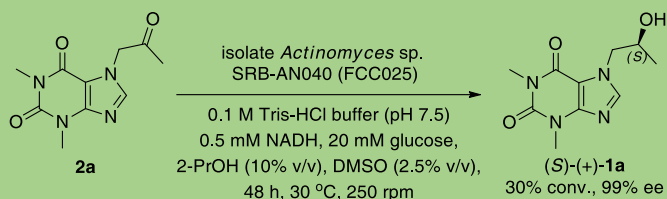
HPLC analytical separation for enantiomers of *rac*-1a on Chiralpak AD-H at 25 °C

HPLC conditions: *n*-hexane-2-PrOH (78:22, v/v); *f*=1.0 mL/min; λ =273 nm; *p*=5.7 MPa

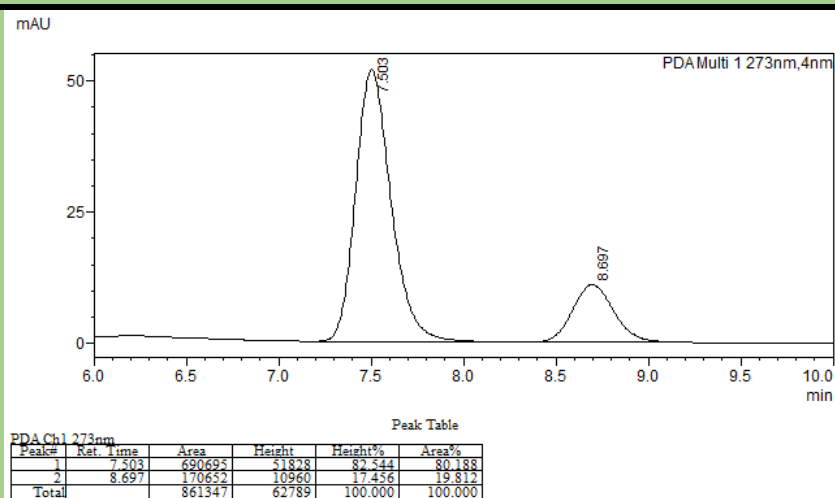
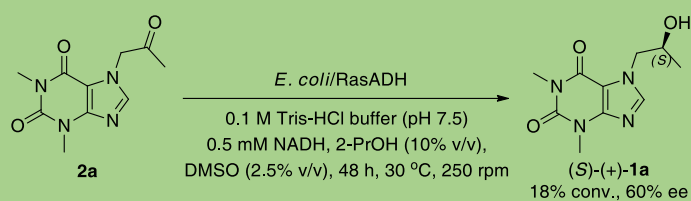


The HPLC analysis of whole microbial cells and ADHs-catalyzed stereoselective reductions of 1,3-dimethyl-7-(2-oxopropyl)-3,7-dihydro-1*H*-purine-2,6-dione (**2a**) –
Screening of the whole-cell biocatalysts

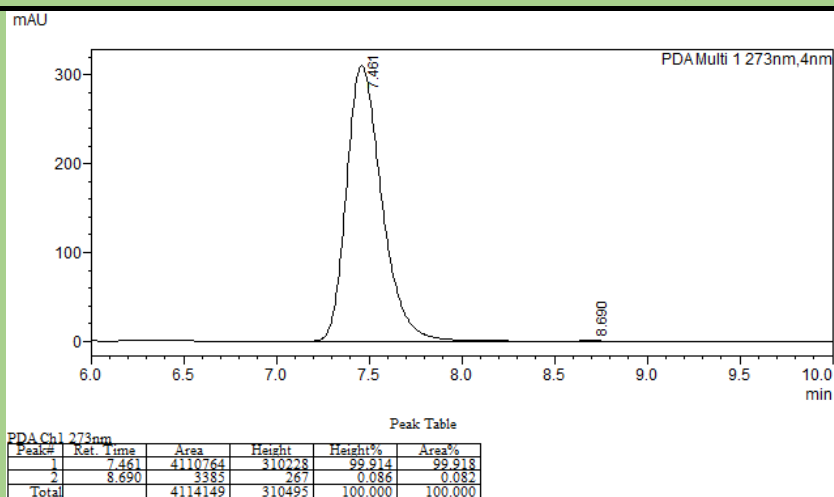
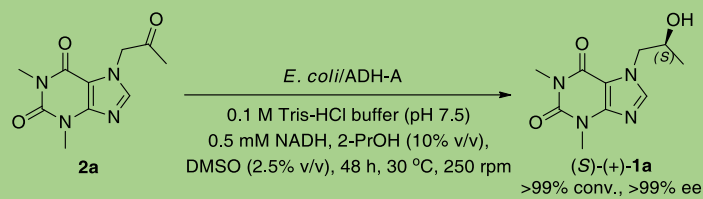
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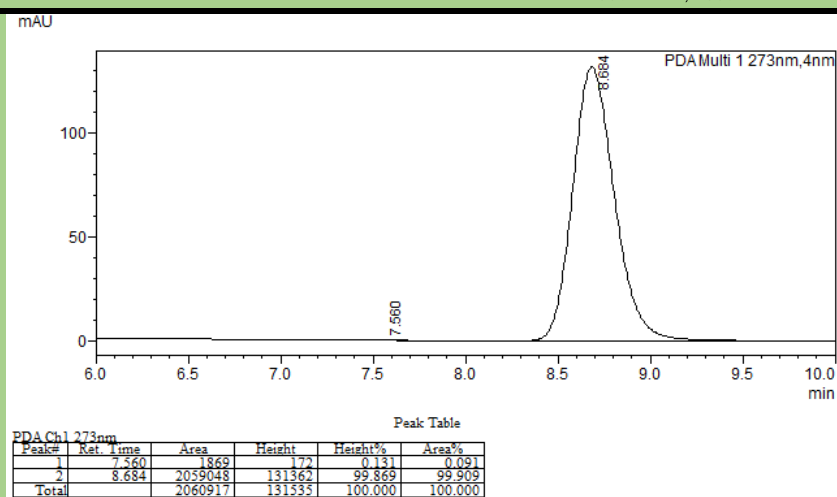
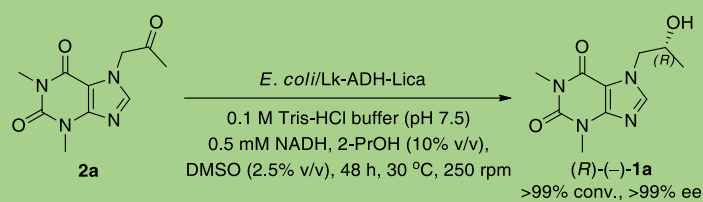
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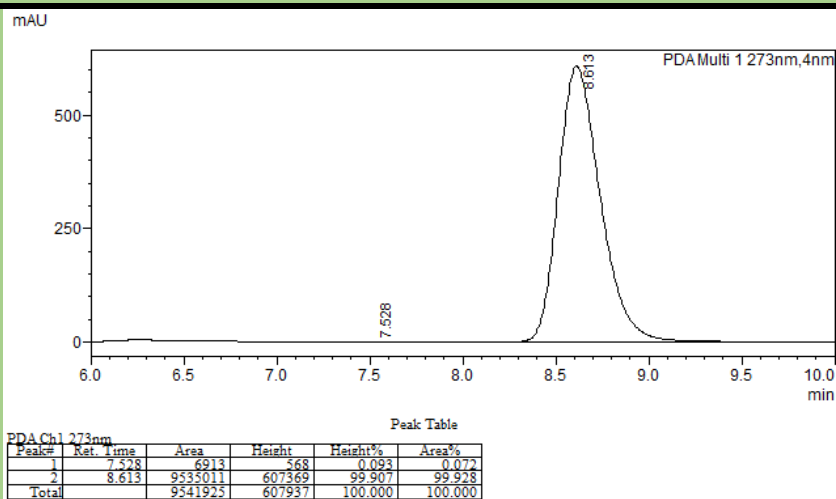
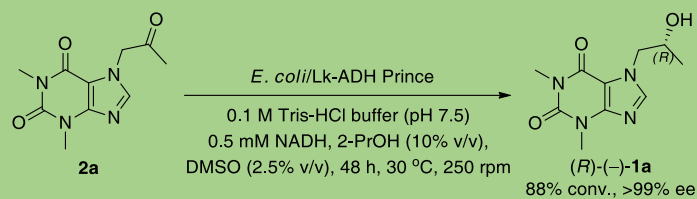
HPLC analysis for the subsequent biocatalytic reaction:



HPLC analysis for the subsequent biocatalytic reaction:



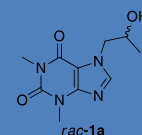
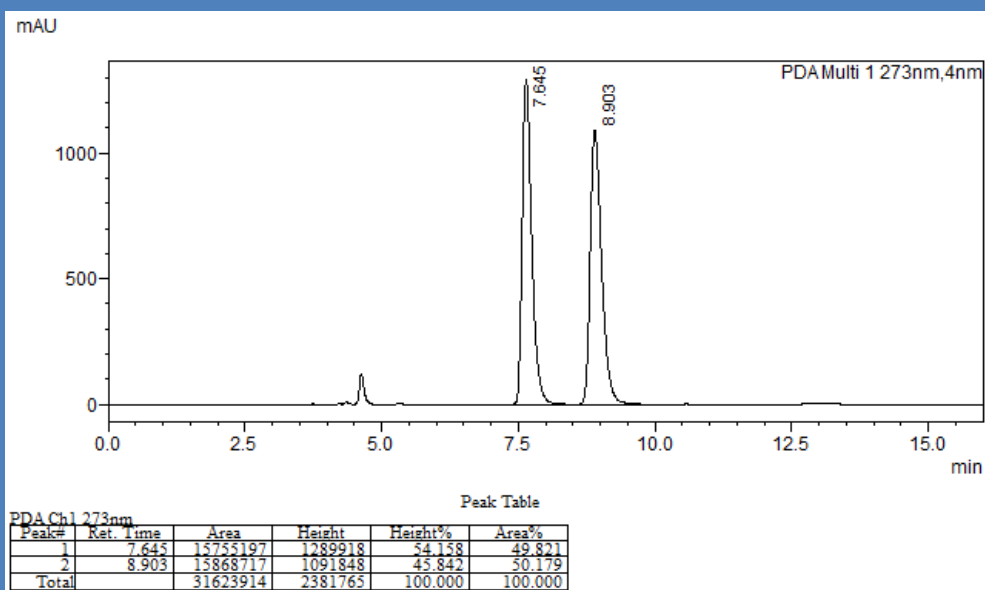
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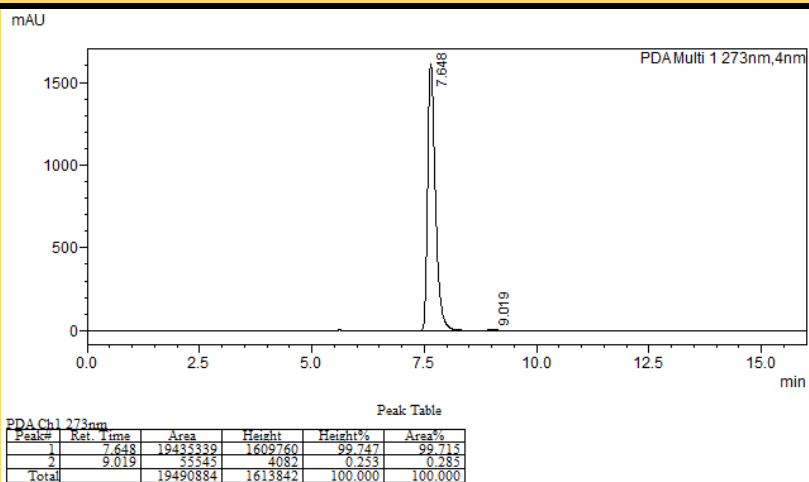
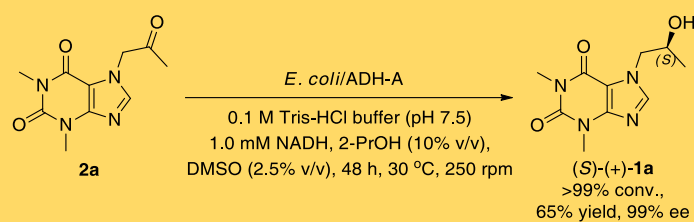
The HPLC analysis of ADHs-catalyzed stereoselective reductions of 1,3-dimethyl-7-(2-oxopropyl)-3,7-dihydro-1H-purine-2,6-dione (2a) – Up-scaling

HPLC analytical separation for enantiomers of *rac*-1a on Chiralpak AD-H at 25 °C

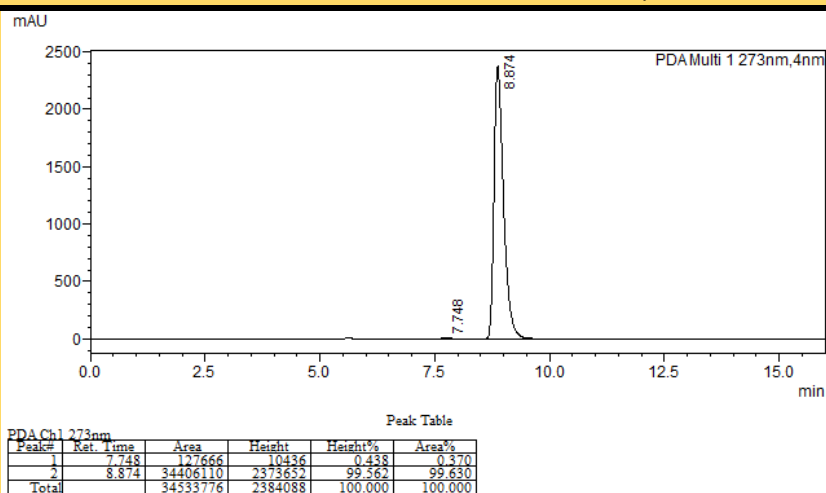
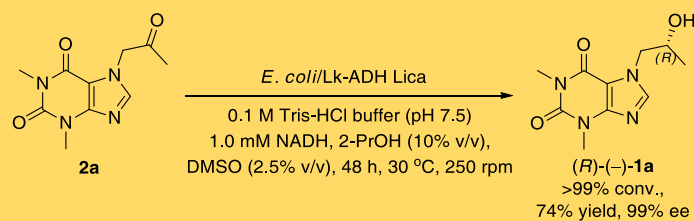
HPLC conditions: *n*-hexane-2-PrOH (78:22, v/v); *f*=1.0 mL/min; λ =273 nm; *p*=5.7 MPa



HPLC analysis for the subsequent biocatalytic reaction:

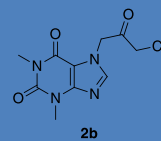
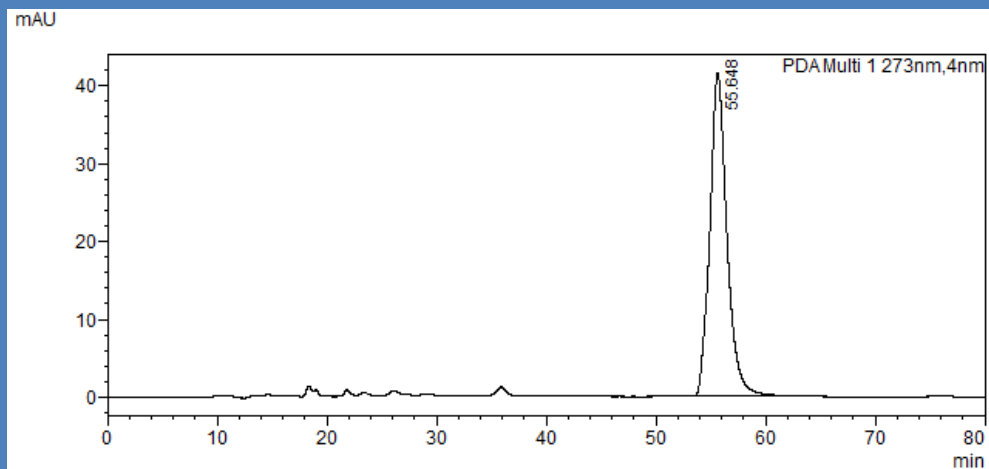


HPLC analysis for the subsequent biocatalytic reaction:



HPLC of 2b on Chiralpak AD-H at 25 °C

HPLC conditions: *n*-hexane-2-PrOH (78:22, v/v); f=0.3 mL/min; λ =273 nm; *p*=1.2 MPa

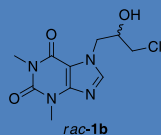
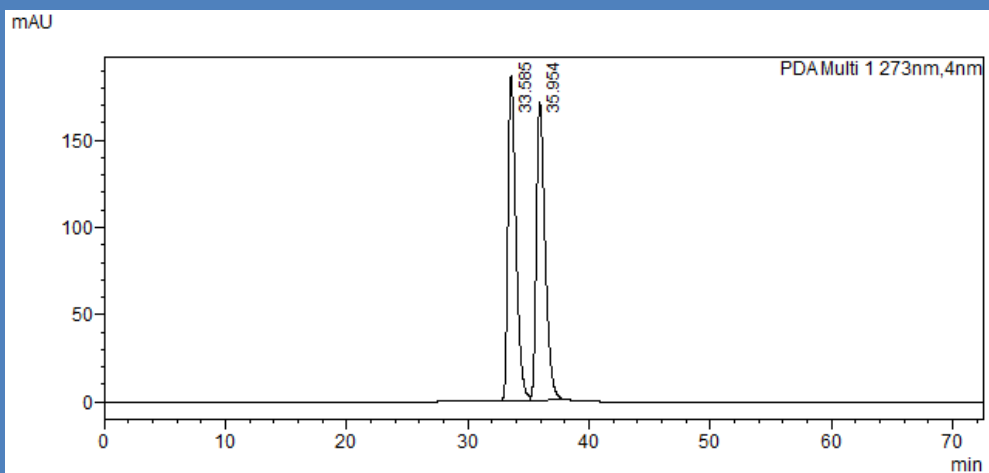


Peak Table

| Peak# | Ret. Time | Area | Height | Height% | Area% |
|-------|-----------|---------|--------|---------|---------|
| 1 | 55.648 | 4505069 | 41463 | 100.000 | 100.000 |
| Total | | 4505069 | 41463 | 100.000 | 100.000 |

HPLC analytical separation for enantiomers of *rac*-1b on Chiralpak AD-H at 25 °C

HPLC conditions: *n*-hexane-2-PrOH (78:22, v/v); f=0.3 mL/min; λ =273 nm; *p*=1.2 MPa

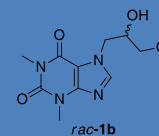
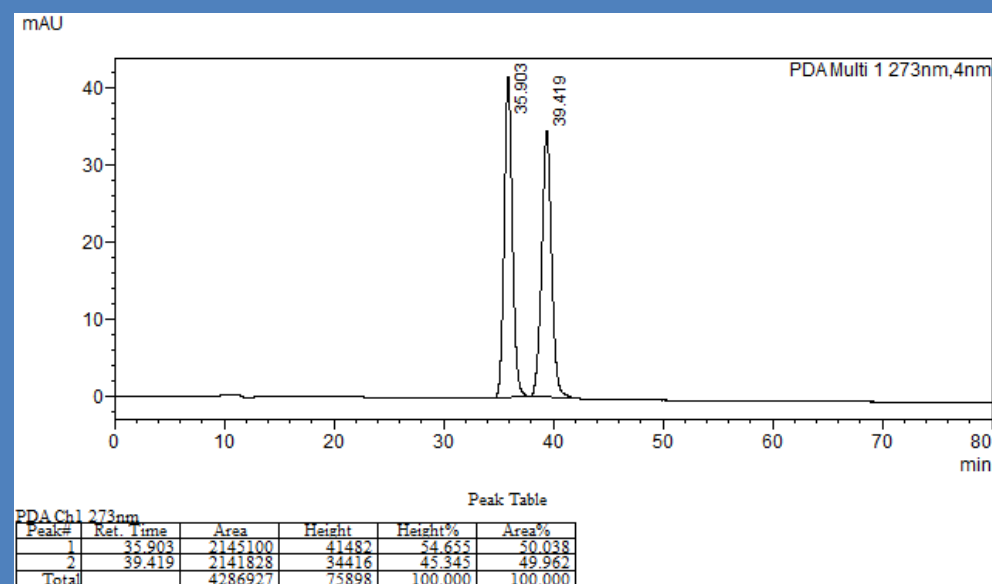


Peak Table

| Peak# | Ret. Time | Area | Height | Height% | Area% |
|-------|-----------|----------|--------|---------|---------|
| 1 | 33.585 | 8558280 | 185933 | 52.132 | 49.863 |
| 2 | 35.954 | 8605216 | 170727 | 47.868 | 50.137 |
| Total | | 17163496 | 356660 | 100.000 | 100.000 |

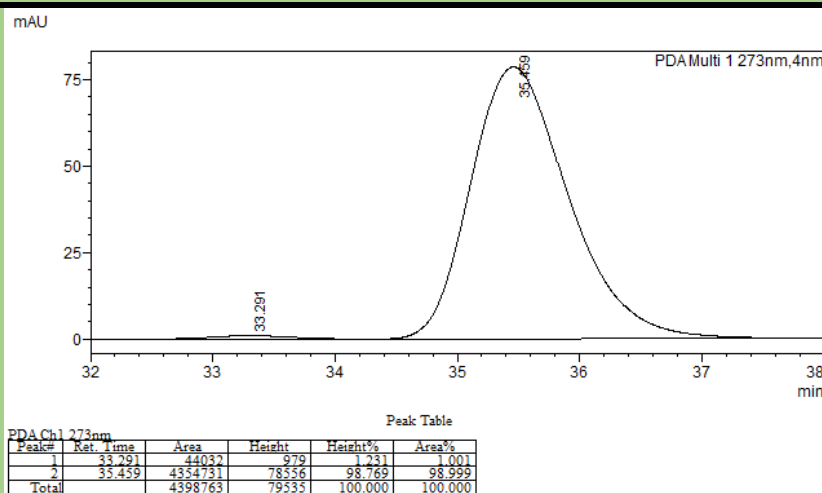
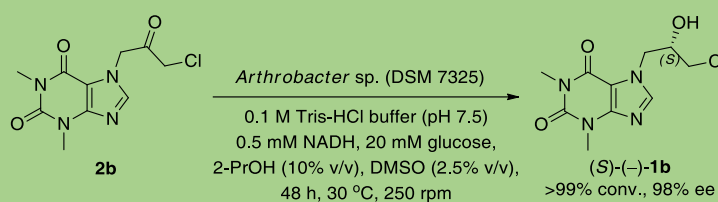
HPLC analytical separation for enantiomers of *rac*-1b on Chiralpak AD-H at 25 °C
(a few months later)

HPLC conditions: *n*-hexane-2-PrOH (78:22, v/v); f=0.3 mL/min; λ=273 nm; p=1.2 MPa

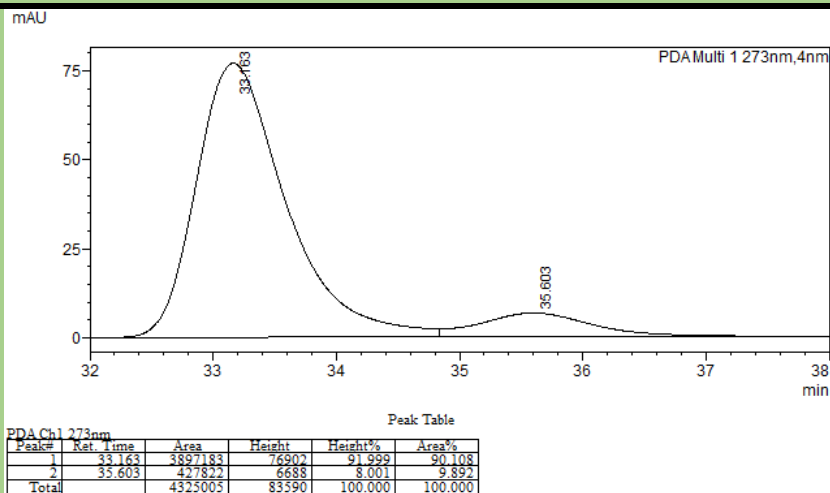
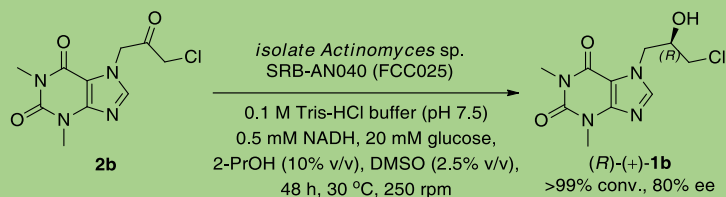


The HPLC analysis of whole microbial cells and ADHs-catalyzed bioreductions of
7-(3-chloro-2-oxopropyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (2b) –
Screening of the whole-cell biocatalysts

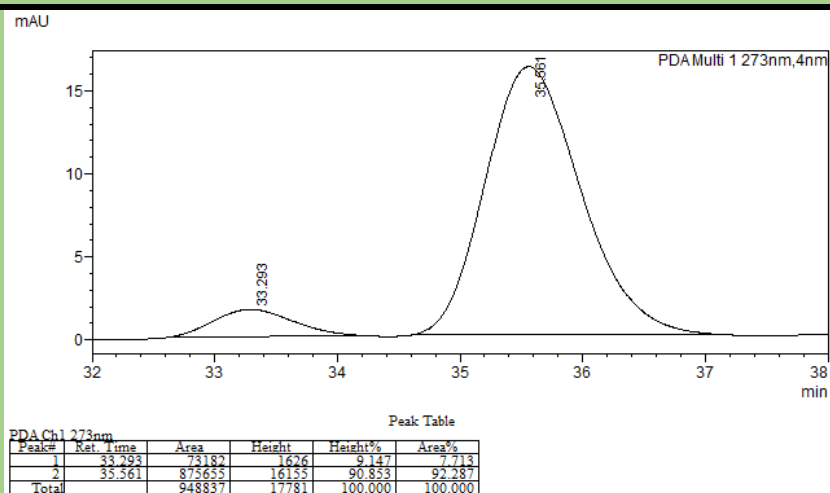
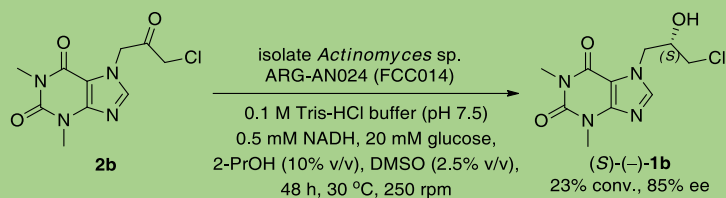
HPLC analysis for the subsequent biocatalytic reaction:



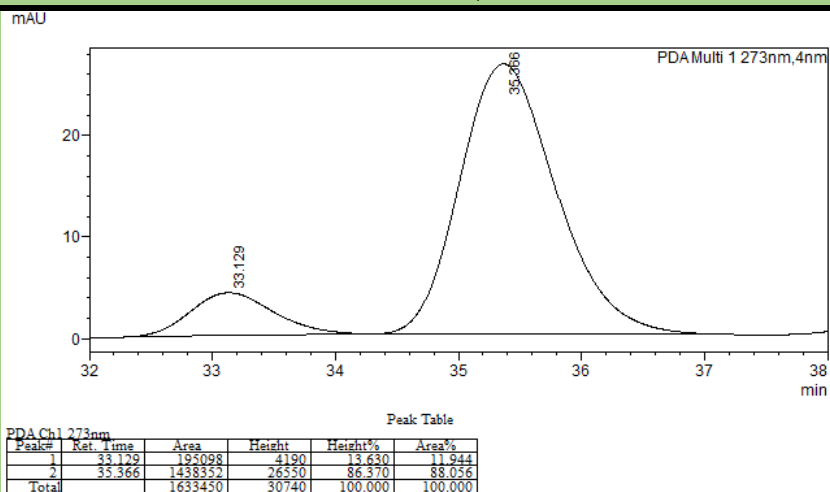
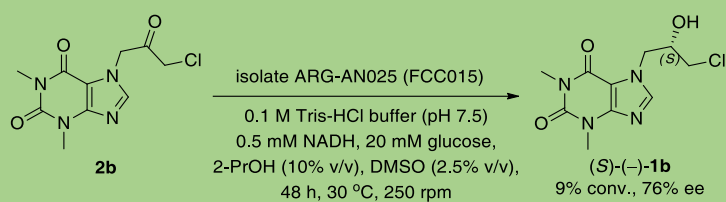
HPLC analysis for the subsequent biocatalytic reaction:



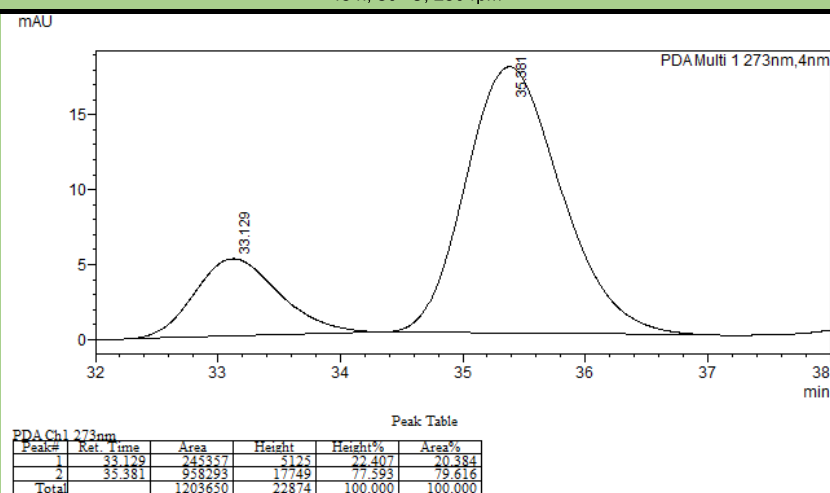
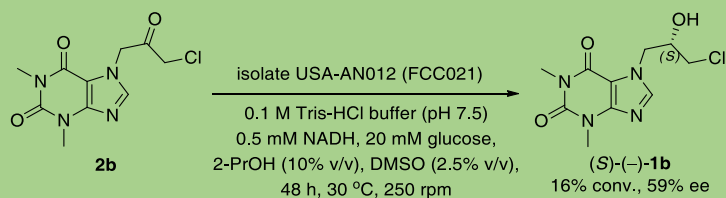
HPLC analysis for the subsequent biocatalytic reaction:



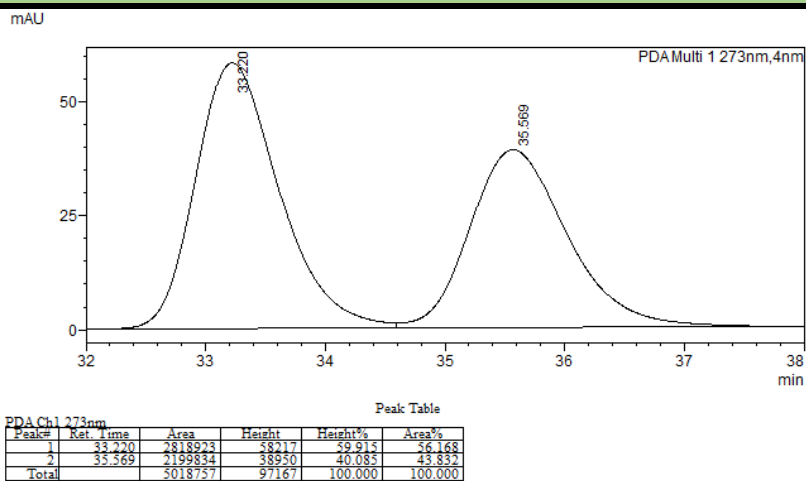
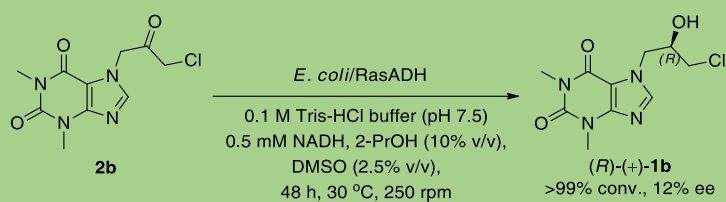
HPLC analysis for the subsequent biocatalytic reaction:



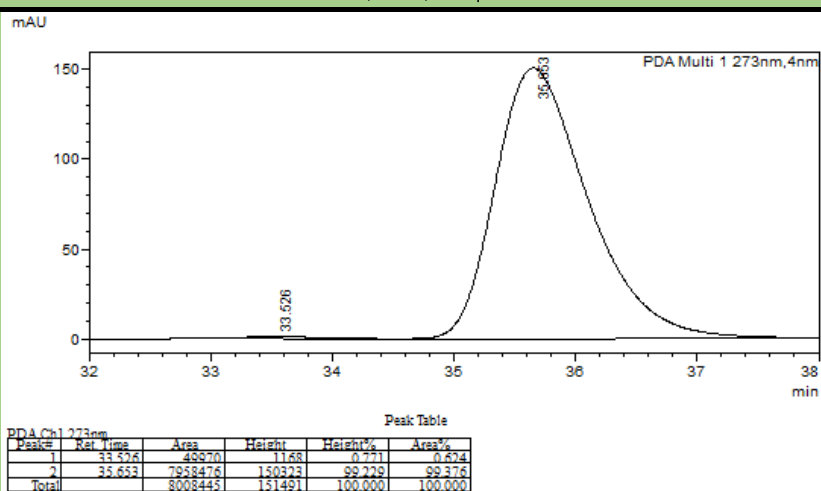
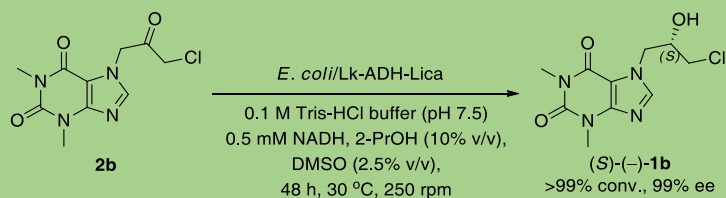
HPLC analysis for the subsequent biocatalytic reaction:



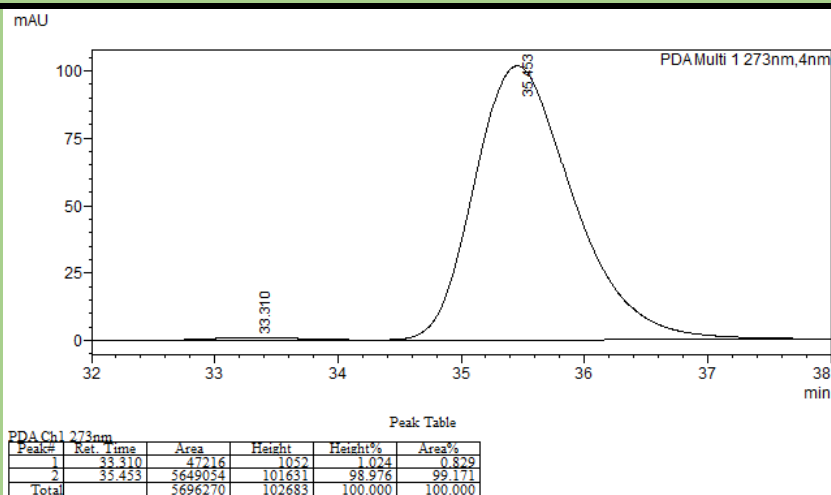
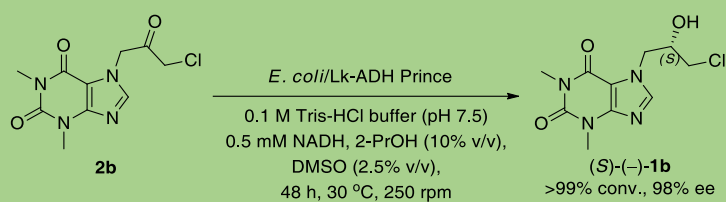
HPLC analysis for the subsequent biocatalytic reaction:



HPLC analysis for the subsequent biocatalytic reaction:

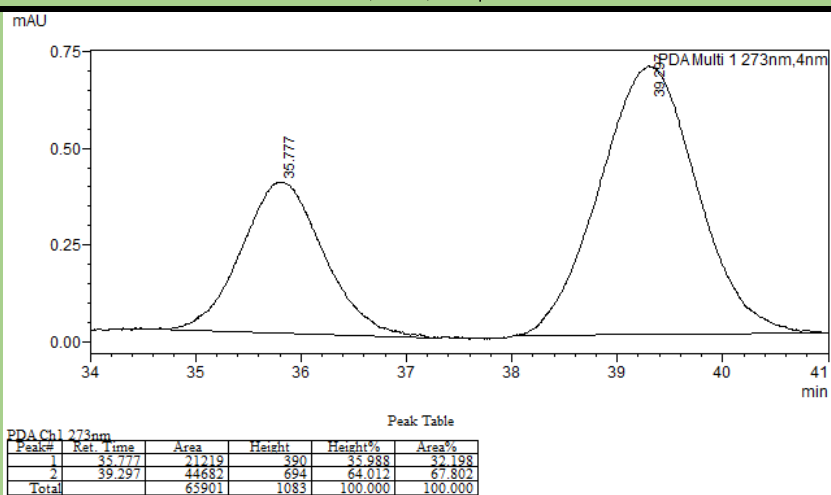
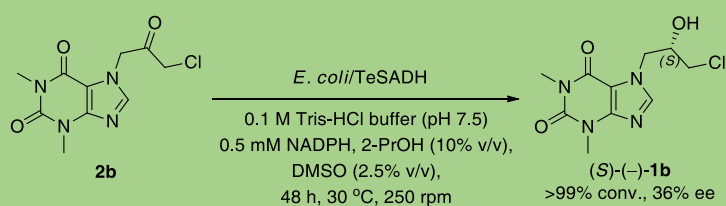


HPLC analysis for the subsequent biocatalytic reaction:

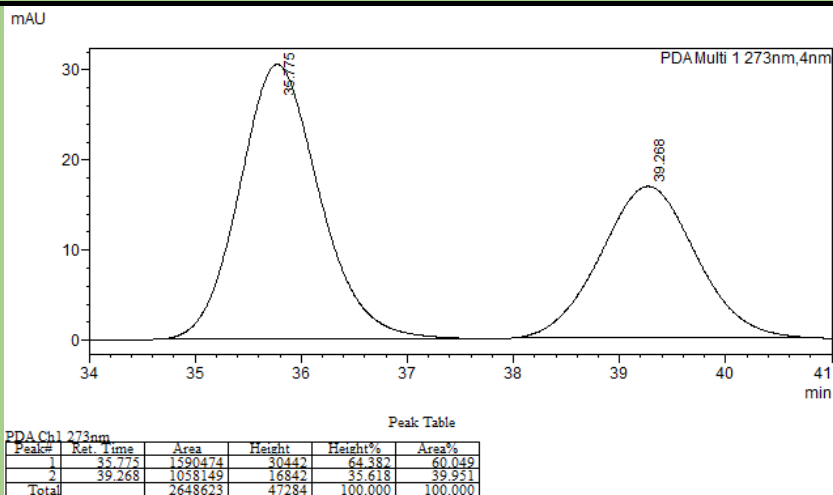
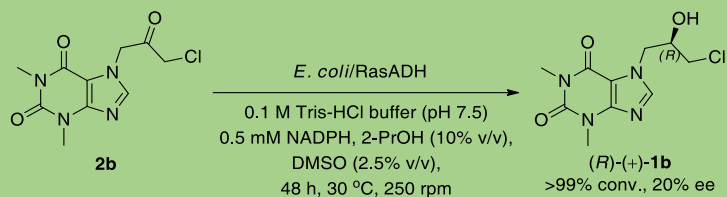


The HPLC analysis of ADHs-catalyzed bioreductions of 7-(3-chloro-2-oxopropyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (2b) in the presence of NADPH – Screening of the whole-cell biocatalysts

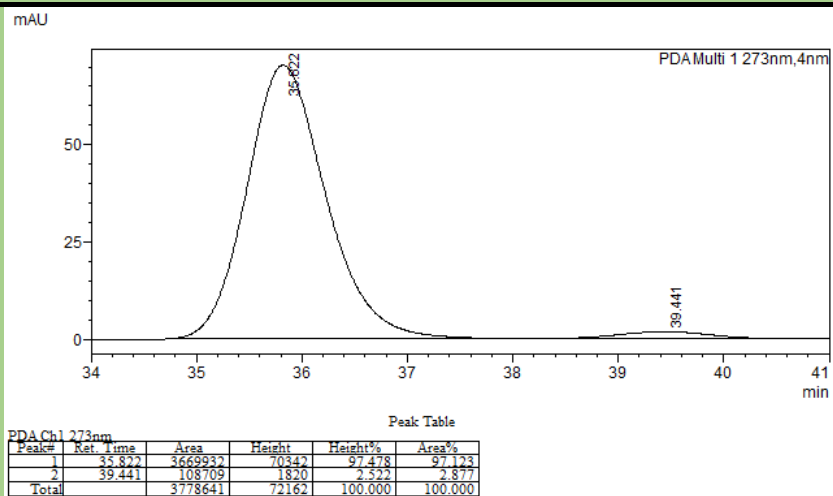
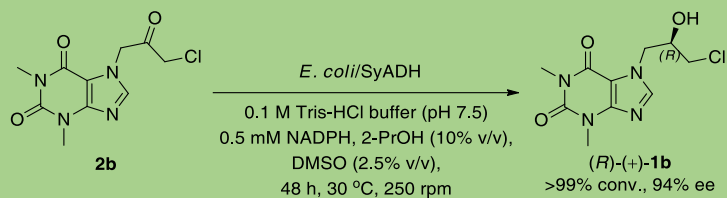
HPLC analysis for the subsequent biocatalytic reaction:



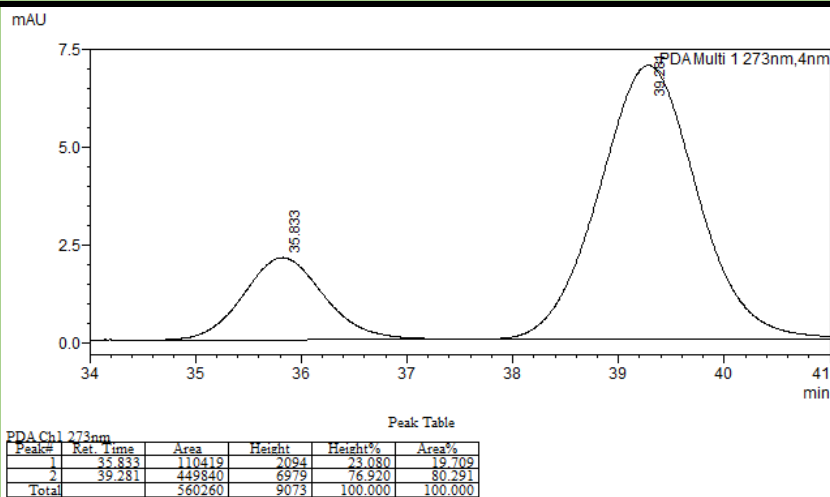
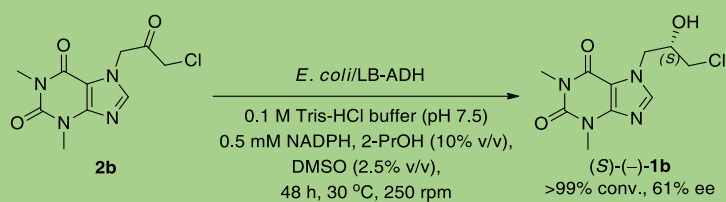
HPLC analysis for the subsequent biocatalytic reaction:



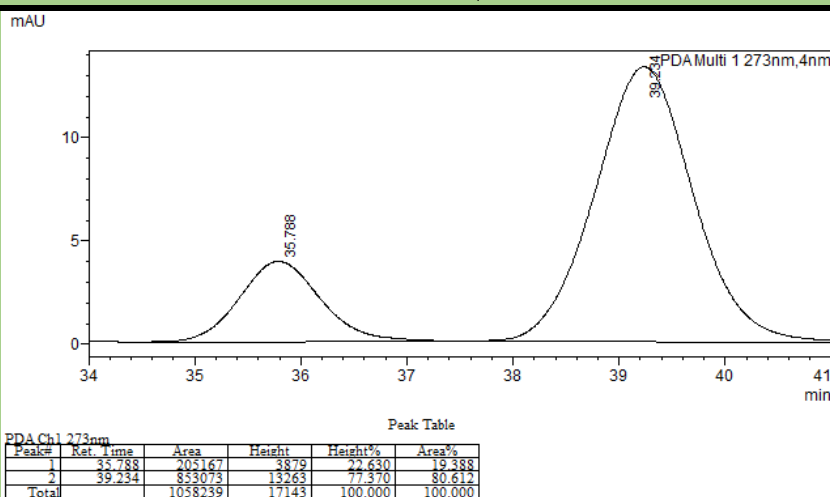
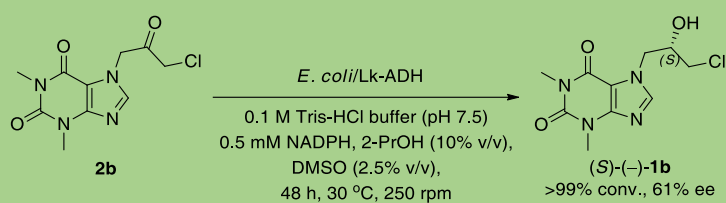
HPLC analysis for the subsequent biocatalytic reaction:



HPLC analysis for the subsequent biocatalytic reaction:



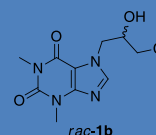
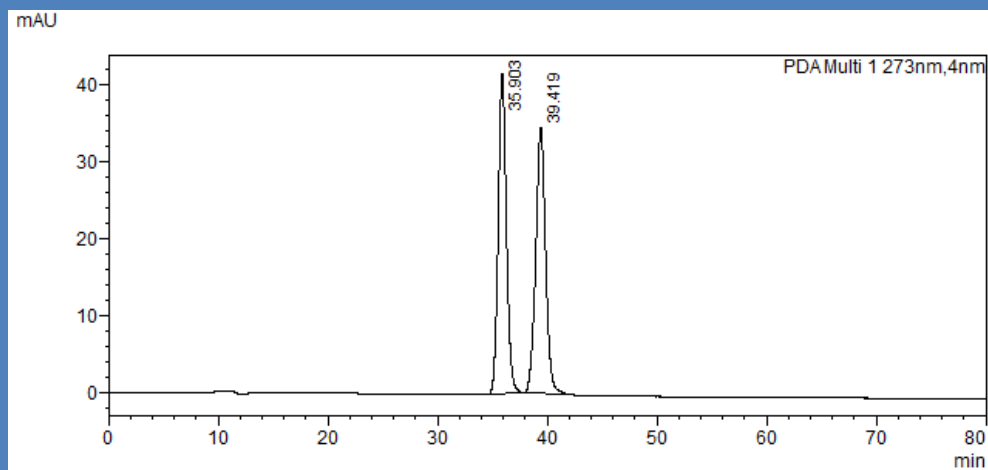
HPLC analysis for the subsequent biocatalytic reaction:



The HPLC analysis of ADHs-catalyzed bioreductions of 7-(3-chloro-2-oxopropyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (**2b**) – *Up-scaling*

HPLC analytical separation for enantiomers of *rac*-**1b** on Chiralpak AD-H at 25 °C

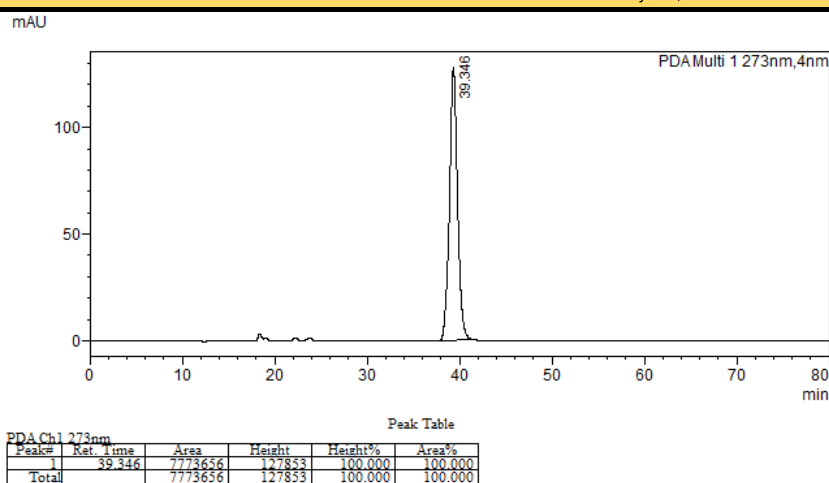
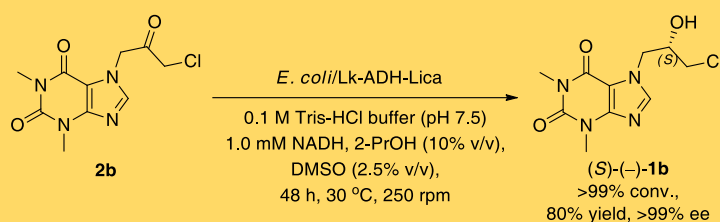
HPLC conditions: *n*-hexane-2-PrOH (78:22, v/v); f=0.7 mL/min; λ=273 nm; p=1.2 MPa



Peak Table

| Peak# | Ret. Time | Area | Height | Height% | Area% |
|-------|-----------|---------|--------|---------|---------|
| 1 | 35.903 | 2145100 | 41482 | 54.655 | 50.038 |
| 2 | 39.419 | 2141828 | 34416 | 45.345 | 49.962 |
| Total | | 4286927 | 75898 | 100.000 | 100.000 |

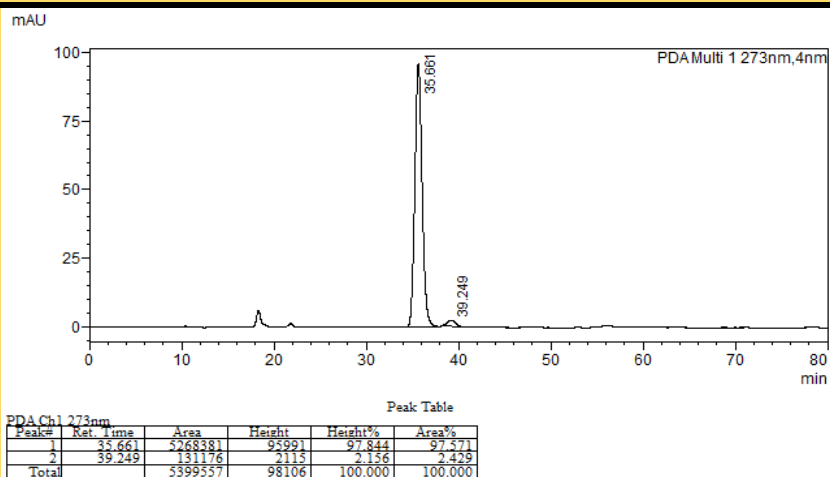
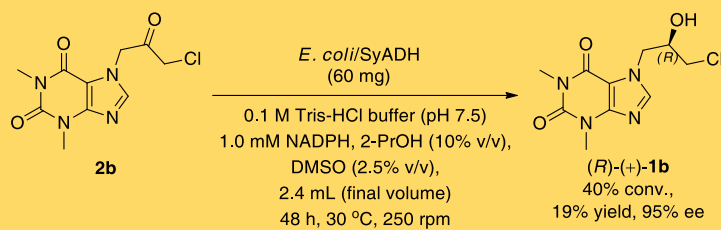
HPLC analysis for the subsequent biocatalytic reaction:



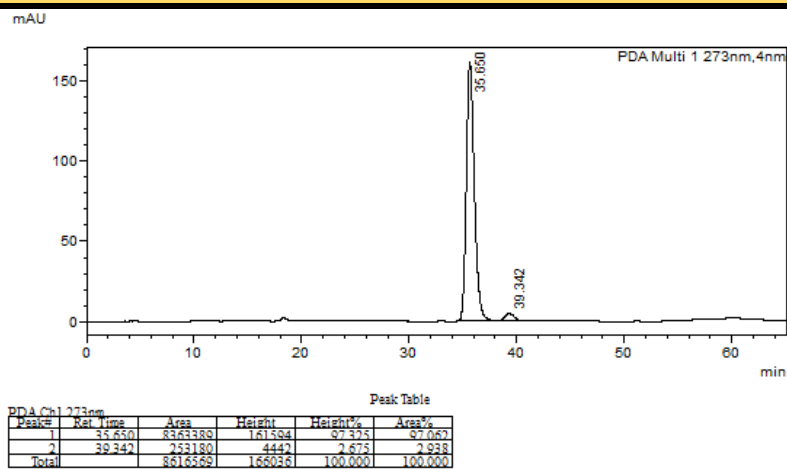
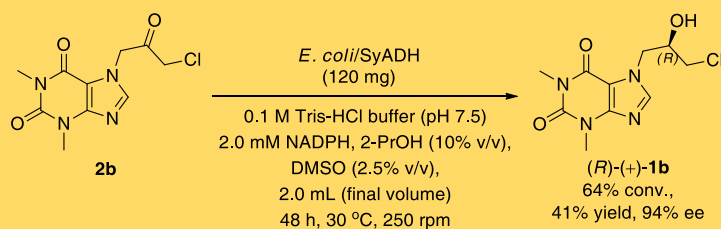
Peak Table

| Peak# | Ret. Time | Area | Height | Height% | Area% |
|-------|-----------|---------|--------|---------|---------|
| 1 | 39.346 | 7773656 | 127853 | 100.000 | 100.000 |
| Total | | 7773656 | 127853 | 100.000 | 100.000 |

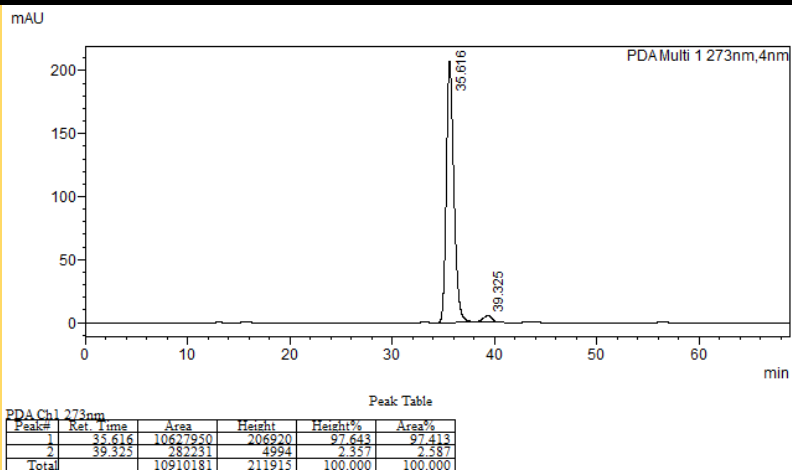
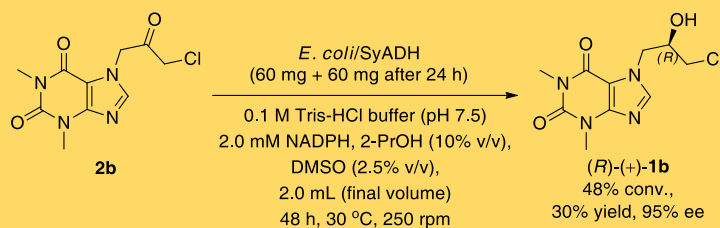
HPLC analysis for the subsequent biocatalytic reaction:



HPLC analysis for the subsequent biocatalytic reaction:

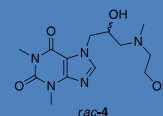
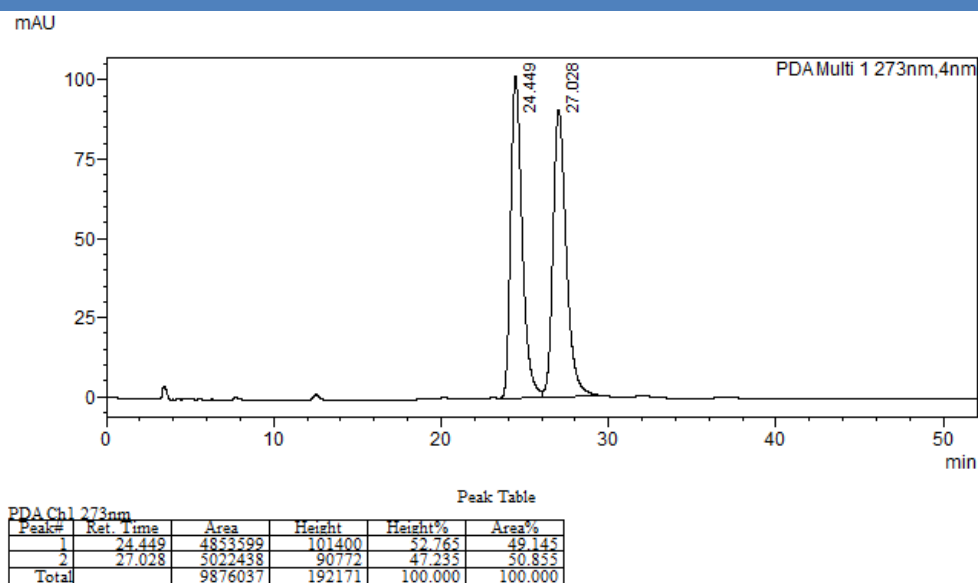


HPLC analysis for the subsequent biocatalytic reaction:



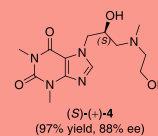
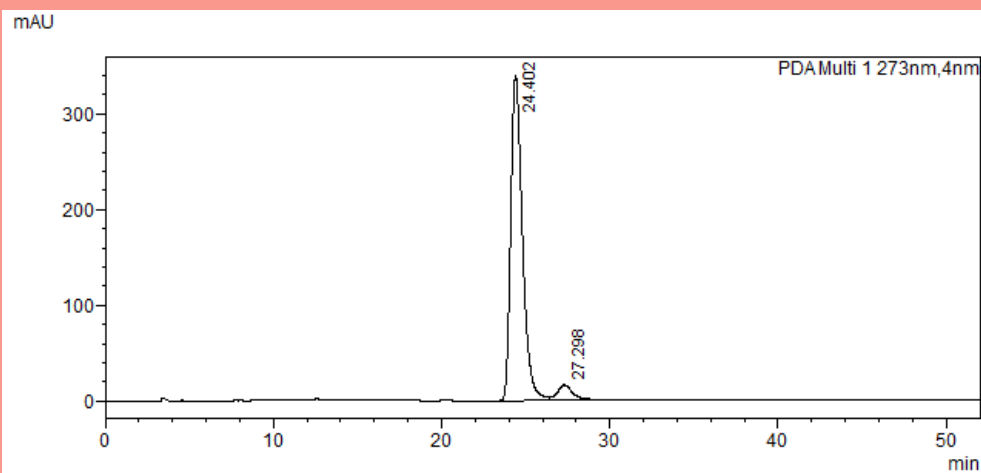
HPLC analytical separation for both enantiomers of xanthinol (*rac*-4) on Lux i-Cellulose-5 at 25 °C

HPLC conditions: *n*-hexane-EtOH-DEA (70:30:0.1, v/v/v); *f*=1.0 mL/min; λ =273 nm; *p*=7.4 MPa



HPLC analysis for (R)-xanthinol [(R)-(-)-4] obtained from the chemical process

HPLC conditions: *n*-hexane-EtOH-DEA (70:30:0.1, v/v/v); *f*=1.0 mL/min; λ =273 nm;
p=7.4 MPa

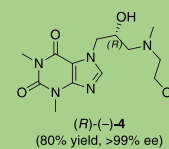
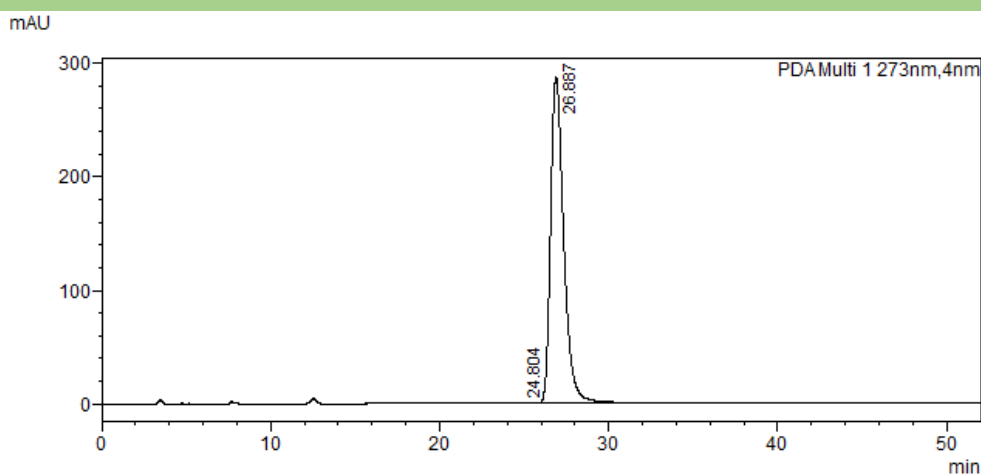


Peak Table

| Peak# | Ret. Time | Area | Height | Height% | Area% |
|-------|-----------|----------|--------|---------|---------|
| 1 | 24.402 | 16383441 | 339113 | 95.599 | 94.180 |
| 2 | 27.298 | 1012373 | 15612 | 4.401 | 5.820 |
| Total | | 17395814 | 354725 | 100.000 | 100.000 |

HPLC analysis for (R)-xanthinol [(R)-(-)-4] obtained from the biocatalytic process

HPLC conditions: *n*-hexane-EtOH-DEA (70:30:0.1, v/v/v); *f*=1.0 mL/min; λ =273 nm;
p=7.4 MPa

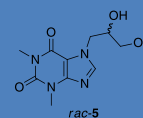
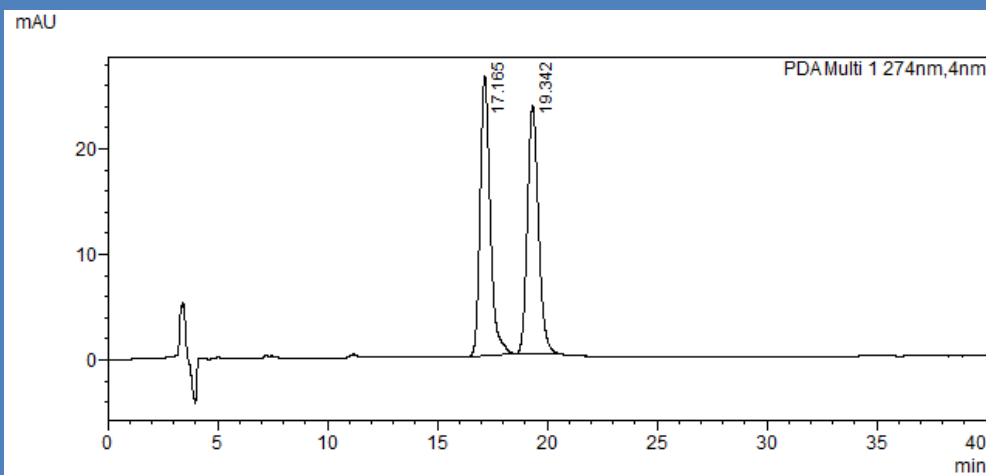


Peak Table

| Peak# | Ret. Time | Area | Height | Height% | Area% |
|-------|-----------|----------|--------|---------|---------|
| 1 | 24.804 | 15081 | 435 | 0.151 | 0.098 |
| 2 | 26.887 | 15408585 | 286500 | 99.849 | 99.902 |
| Total | | 15423667 | 286935 | 100.000 | 100.000 |

HPLC analytical separation for both enantiomers of diprophylline (*rac*-5) on Lux i-Cellulose-5 at 30 °C

HPLC conditions: *n*-hexane-EtOH (70:30, v/v); *f*=1.0 mL/min; λ =273 nm; *p*=7.2 MPa

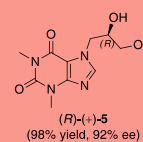
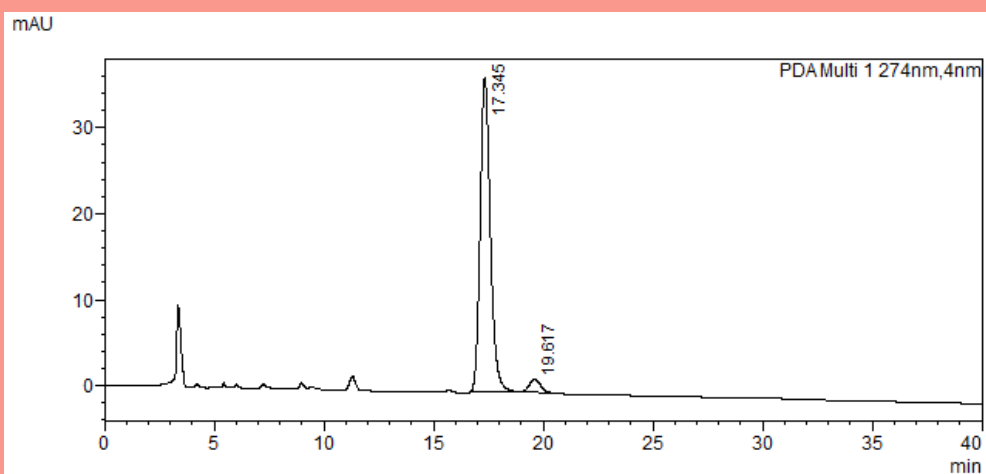


Peak Table

| Peak# | Ret. Time | Area | Height | Height% | Area% |
|-------|-----------|---------|--------|---------|---------|
| 1 | 17.165 | 850348 | 26488 | 52.942 | 50.646 |
| 2 | 19.342 | 828651 | 23544 | 47.058 | 49.354 |
| Total | | 1679000 | 50033 | 100.000 | 100.000 |

HPLC analysis for (*R*)-diprophylline [(*R*)-(+)-5] obtained from the chemical process

HPLC conditions: *n*-hexane-EtOH (73:30, v/v); *f*=1.0 mL/min; λ =273 nm; *p*=7.2 MPa

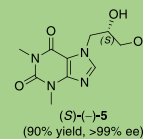
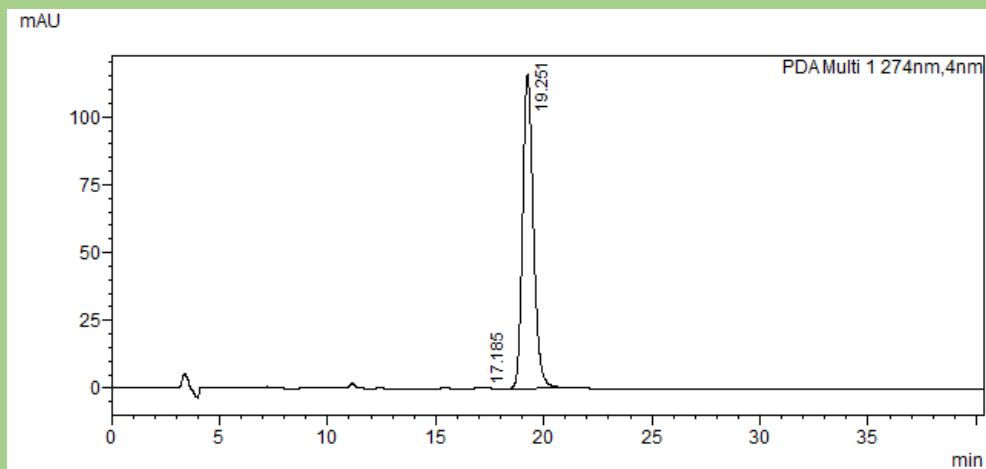


Peak Table

| Peak# | Ret. Time | Area | Height | Height% | Area% |
|-------|-----------|---------|--------|---------|---------|
| 1 | 17.345 | 1181483 | 36519 | 96.131 | 95.993 |
| 2 | 19.617 | 49312 | 1470 | 3.869 | 4.007 |
| Total | | 1230796 | 37989 | 100.000 | 100.000 |

HPLC analysis for (S)-diprophylline [(S)-(-)-5] obtained from the biocatalytic process

HPLC conditions: *n*-hexane-EtOH (73:30, v/v); *f*=1.0 mL/min; λ =273 nm; *p*=7.2 MPa

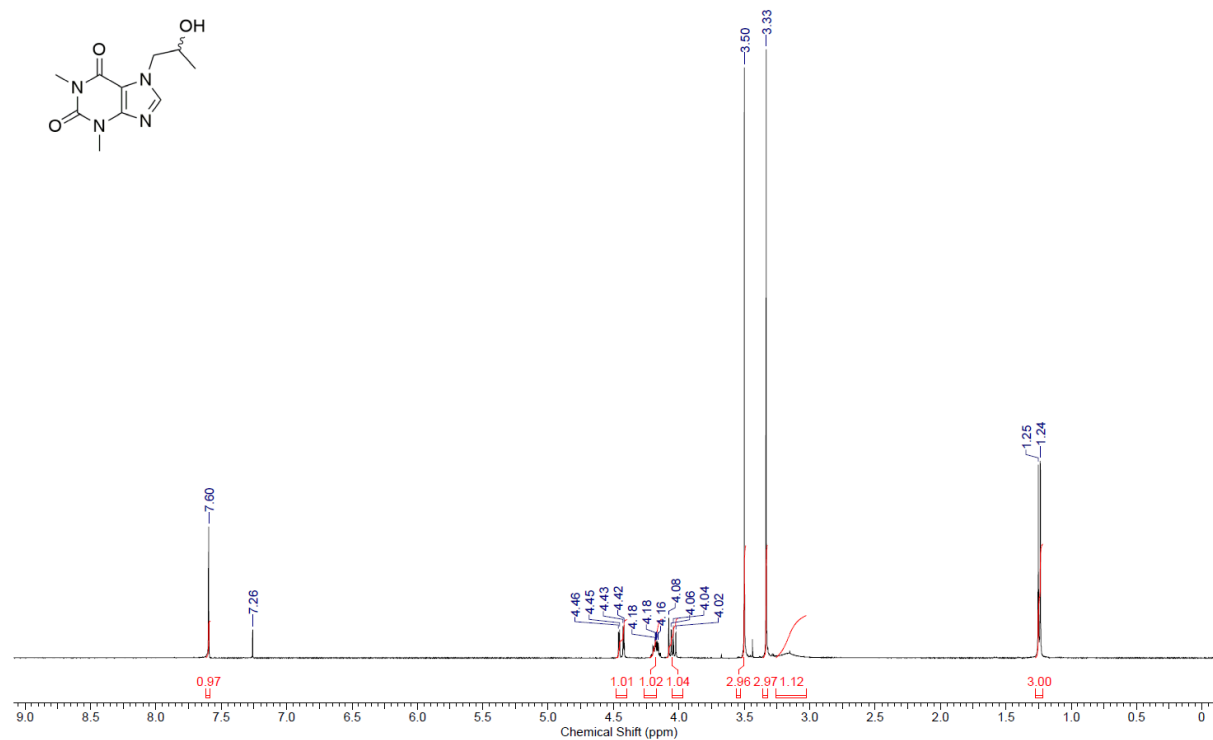


Peak Table

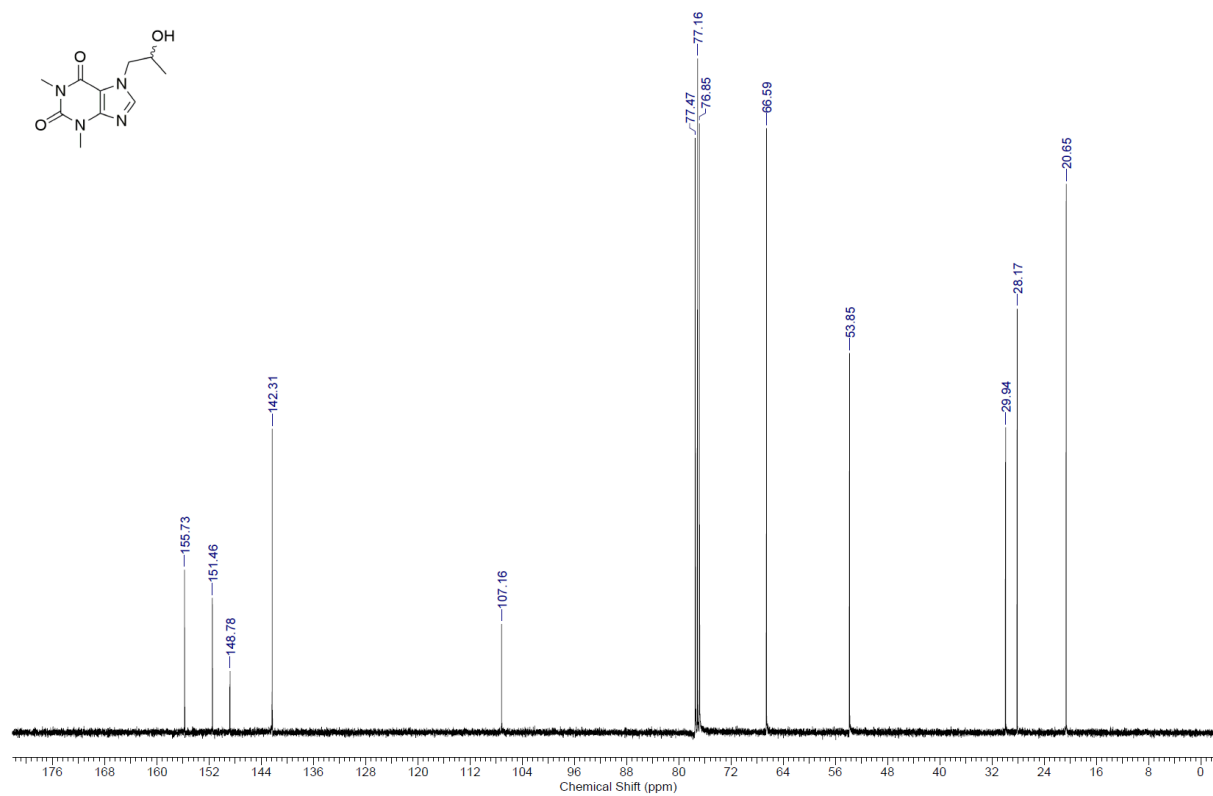
| Peak# | Ret. Time | Area | Height | Height% | Area% |
|-------|-----------|---------|--------|---------|---------|
| 1 | 17.185 | 6608 | 288 | 0.248 | 0.164 |
| 2 | 19.251 | 4011575 | 115637 | 99.752 | 99.836 |
| Total | | 4018184 | 115925 | 100.000 | 100.000 |

7-(2-Hydroxypropyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (proxiphylline, rac-1a)

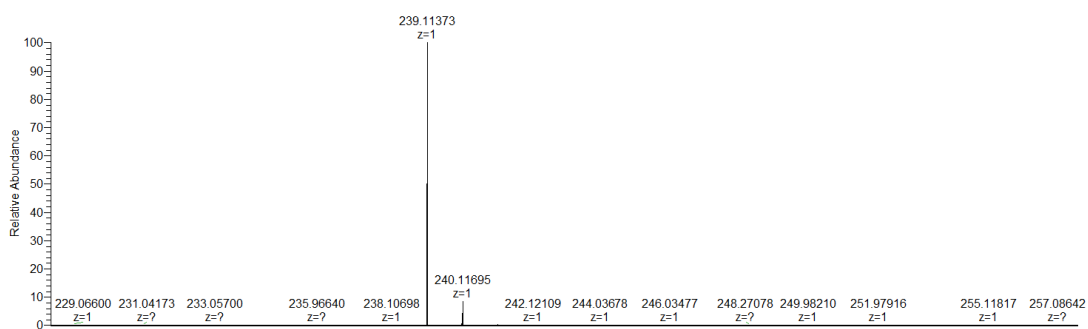
¹H NMR spectrum of *rac-1a* (500 MHz, CDCl₃)



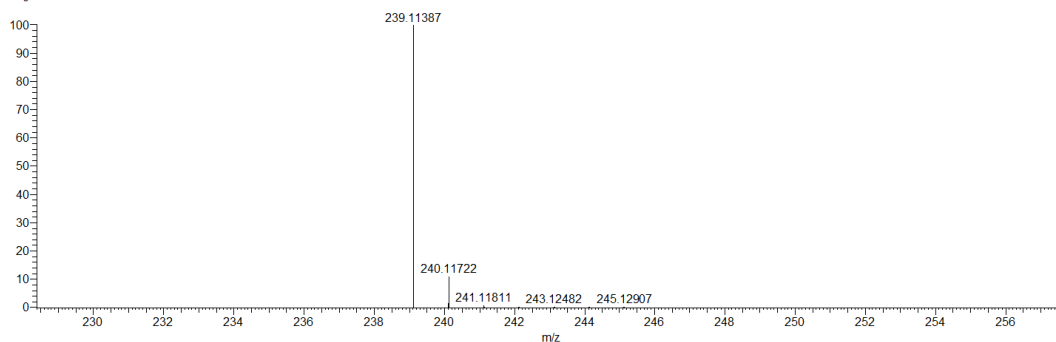
¹³C NMR spectrum of *rac-1a* (126 MHz, CDCl₃)



FTMS spectrum of *rac-1a* (ESI-TOF)



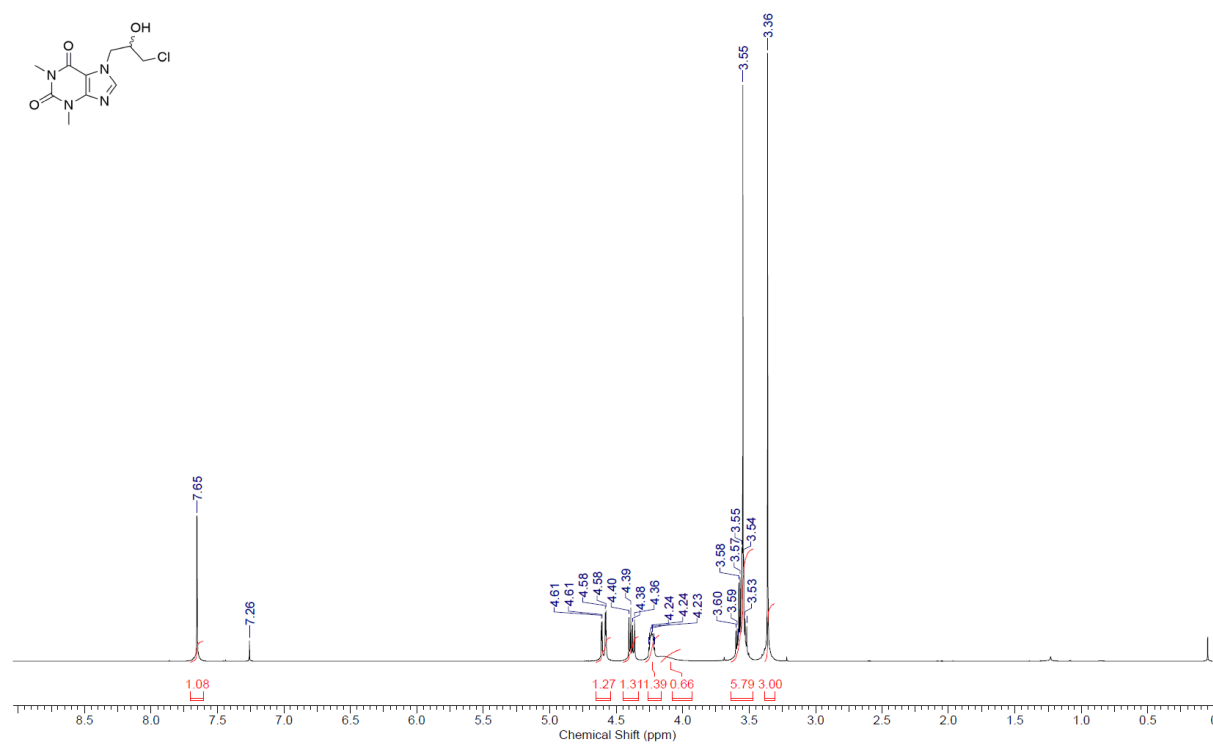
NL:
1.88E8
220214_AR_2ea#6-
72 RT: 0.05-0.63 AV:
67 T: FTMS + p ESI
Full ms
[80.0000-1200.0000]



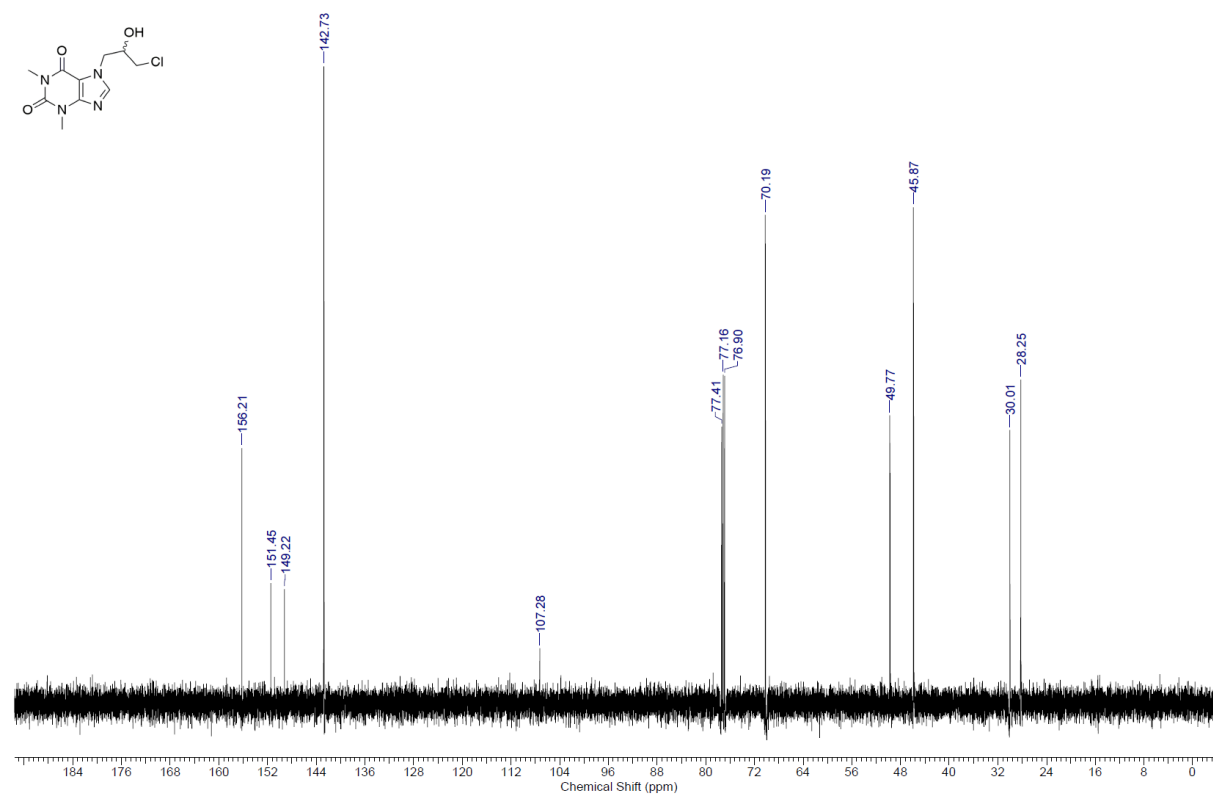
NL:
8.77E5
C₁₀H₁₅N₄O₃
C₁₀H₁₅N₄O₃
pa Chrg 1

7-(3-Chloro-2-hydroxypropyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (*rac-1b*)

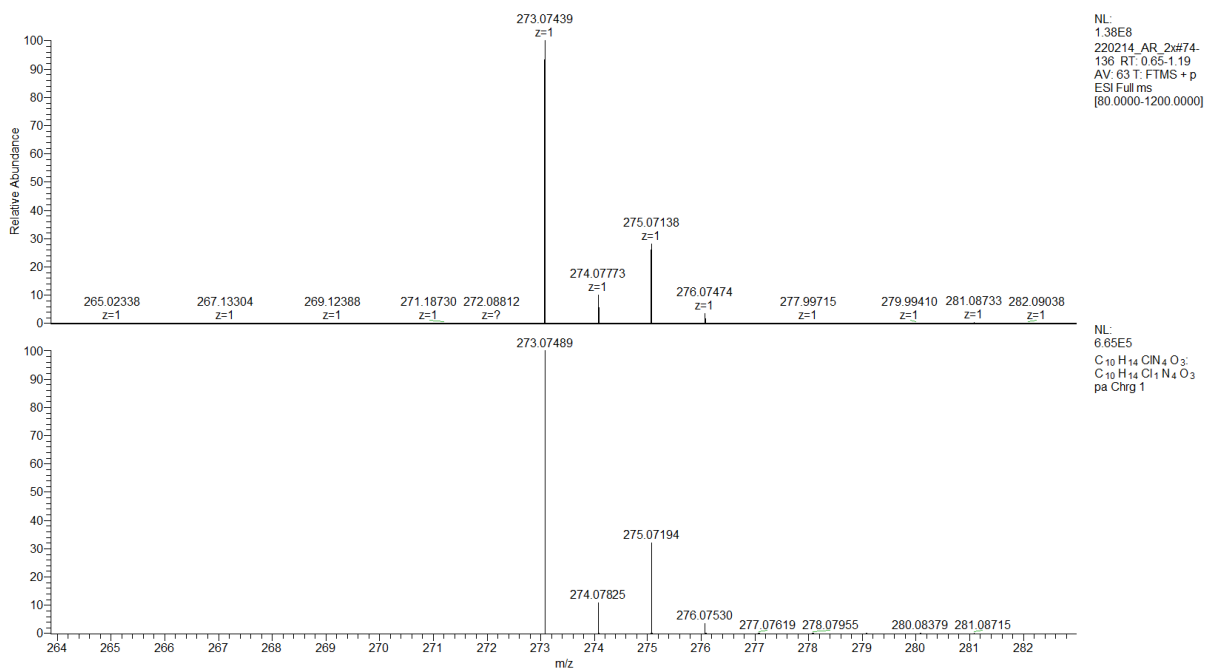
¹H NMR spectrum of *rac-1b* (500 MHz, CDCl₃)



¹³C NMR spectrum of *rac-1b* (126 MHz, CDCl₃)

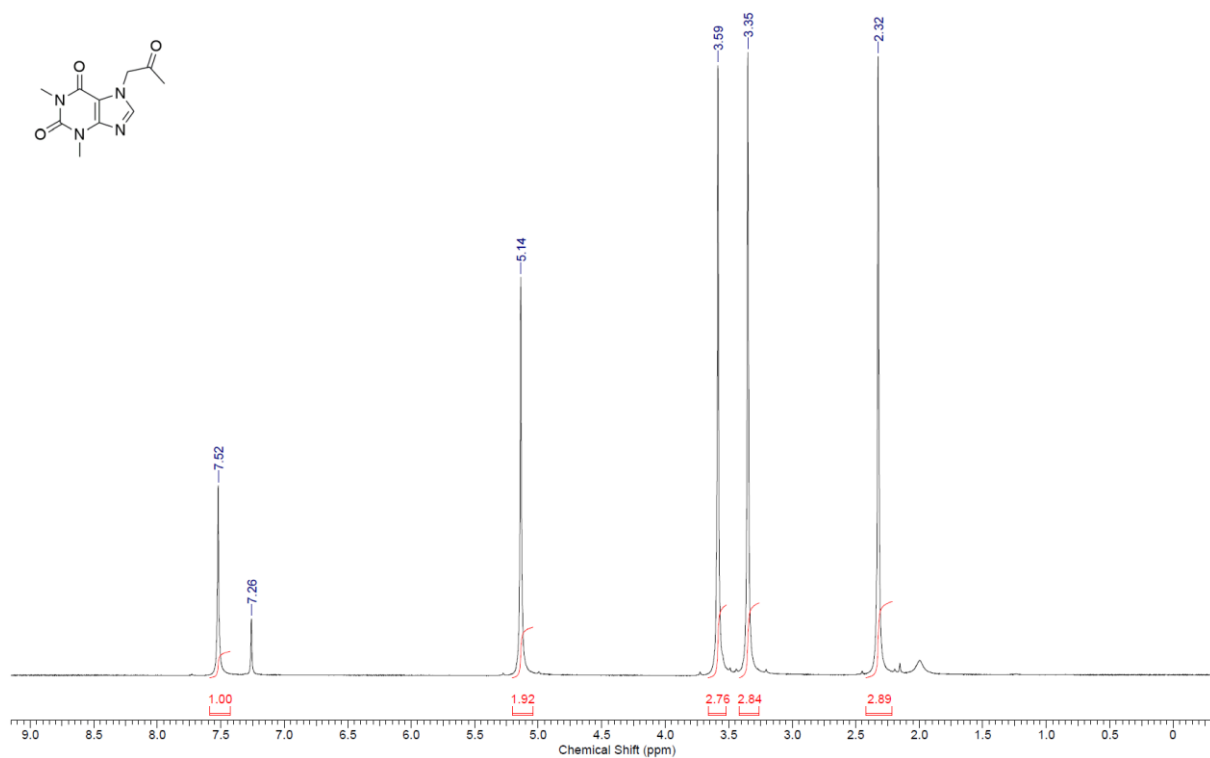


FTMS spectrum of *rac-1b* (ESI-TOF)

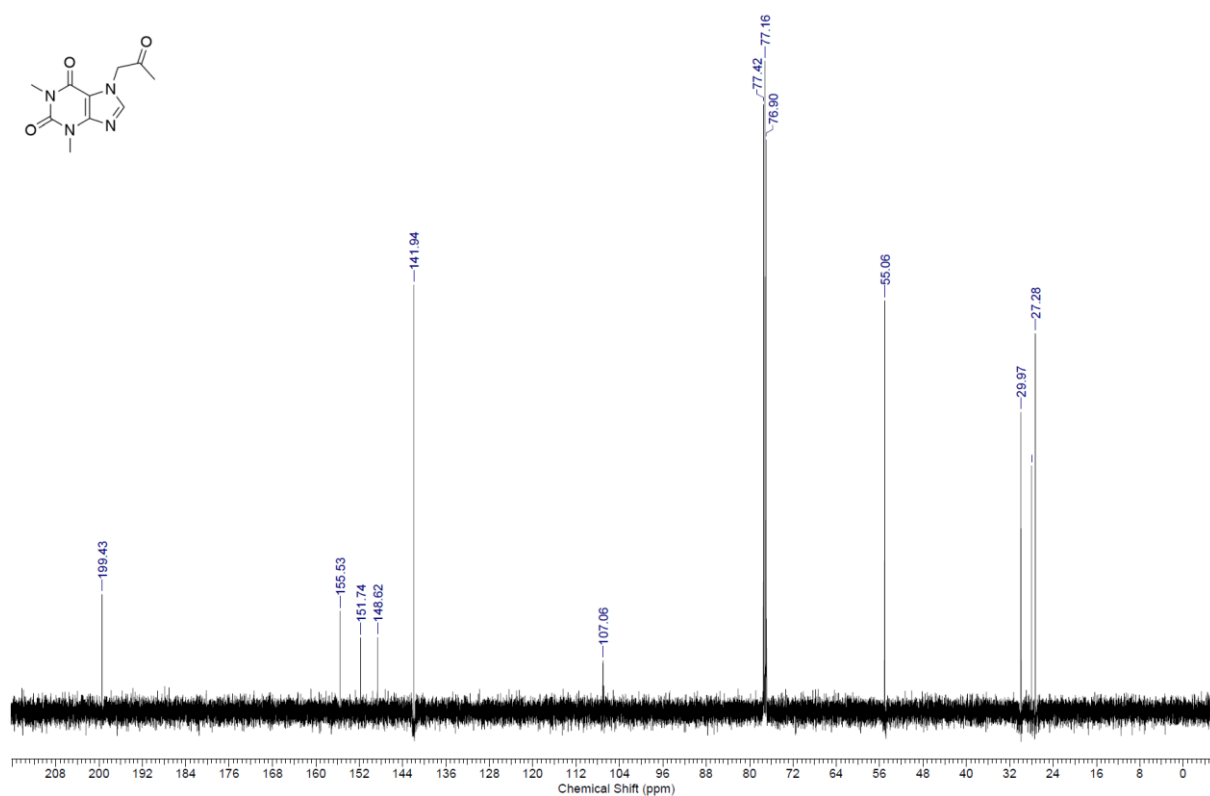


1,3-Dimethyl-7-(2-oxopropyl)-3,7-dihydro-1H-purine-2,6-dione (2a)

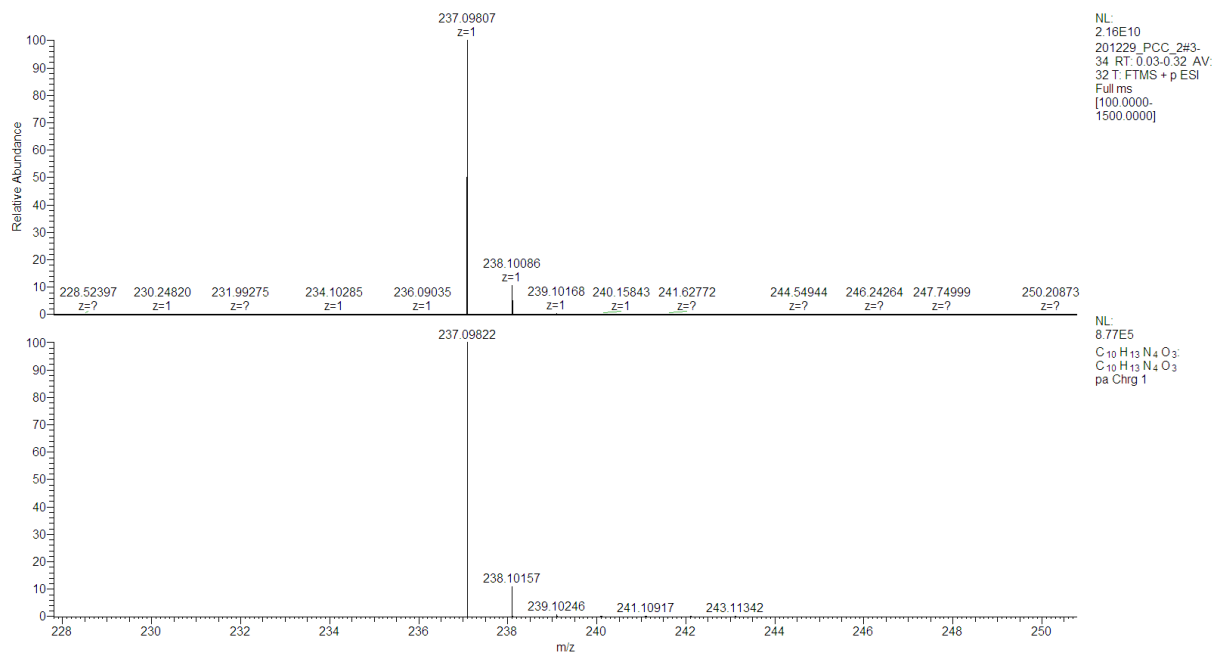
¹H NMR spectrum of **2a** (500 MHz, CDCl₃)



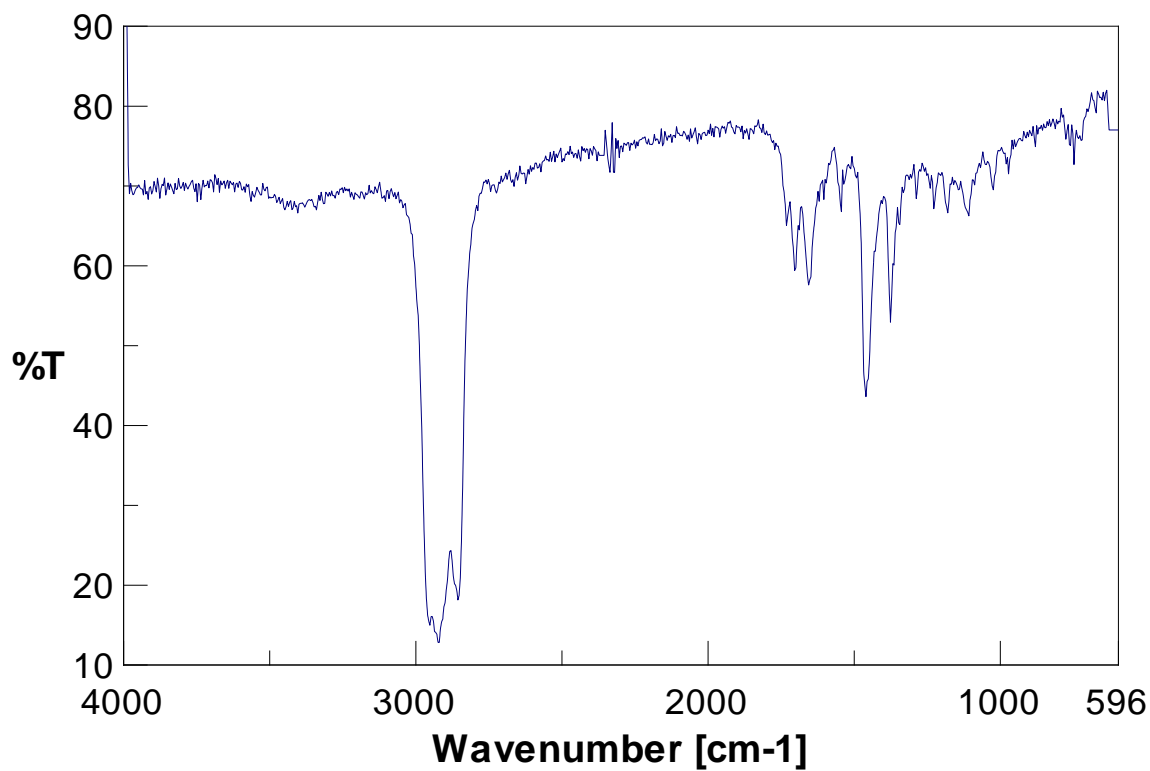
¹³C NMR spectrum of **2a** (126 MHz, CDCl₃)



FTMS spectrum of **2a** (ESI-TOF)

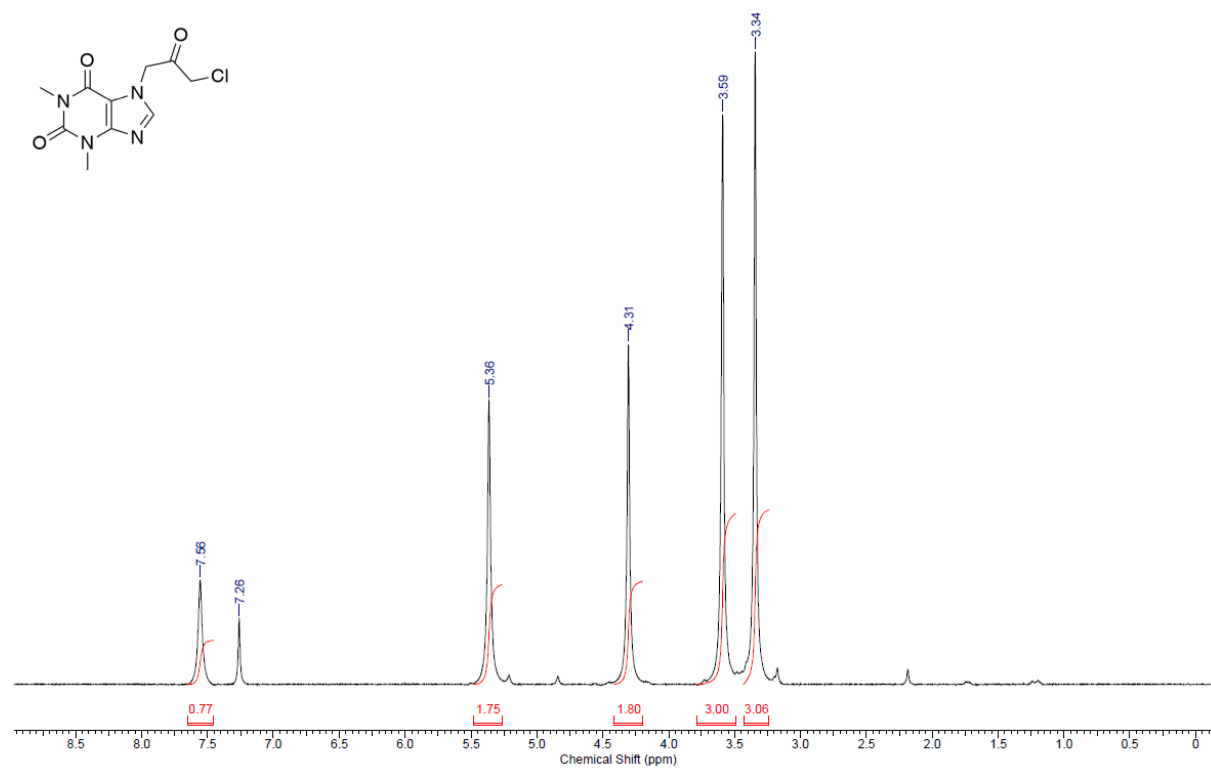


IR spectrum of **2a** (Mineral oil, Nujol)

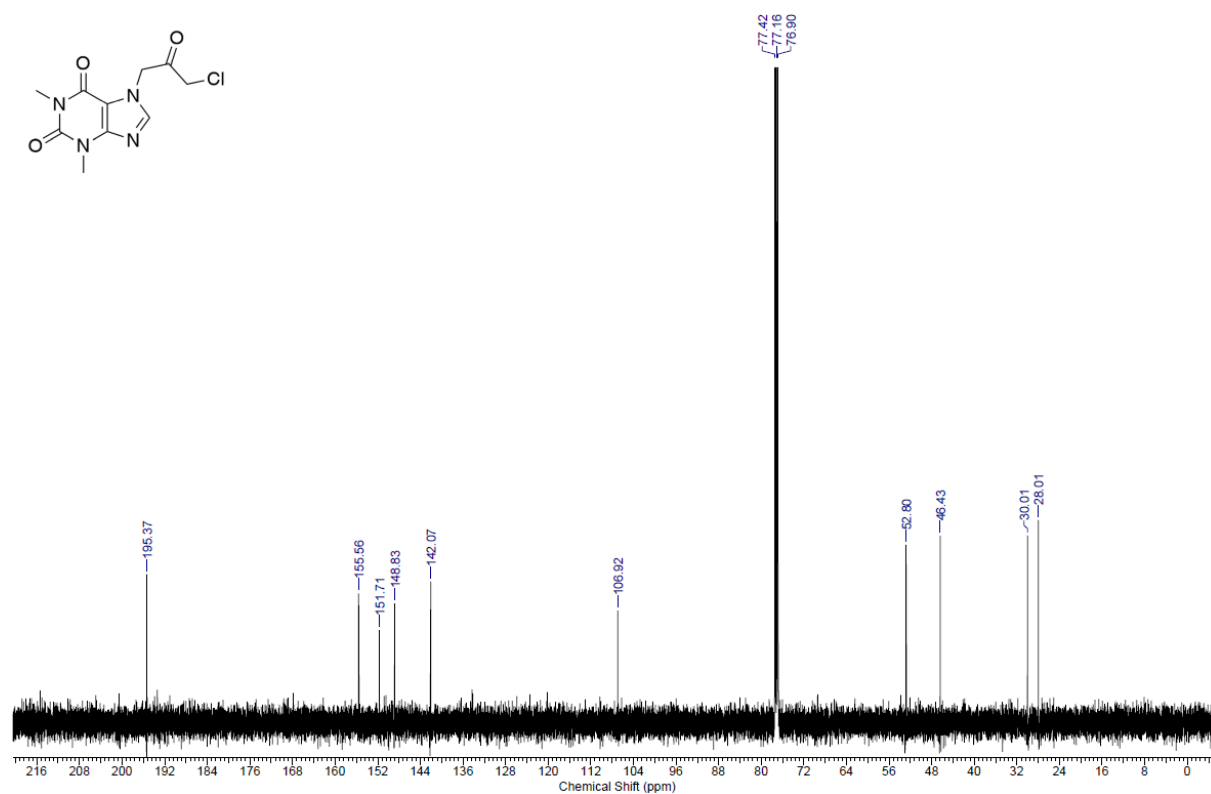


7-(3-Chloro-2-oxopropyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (2b)

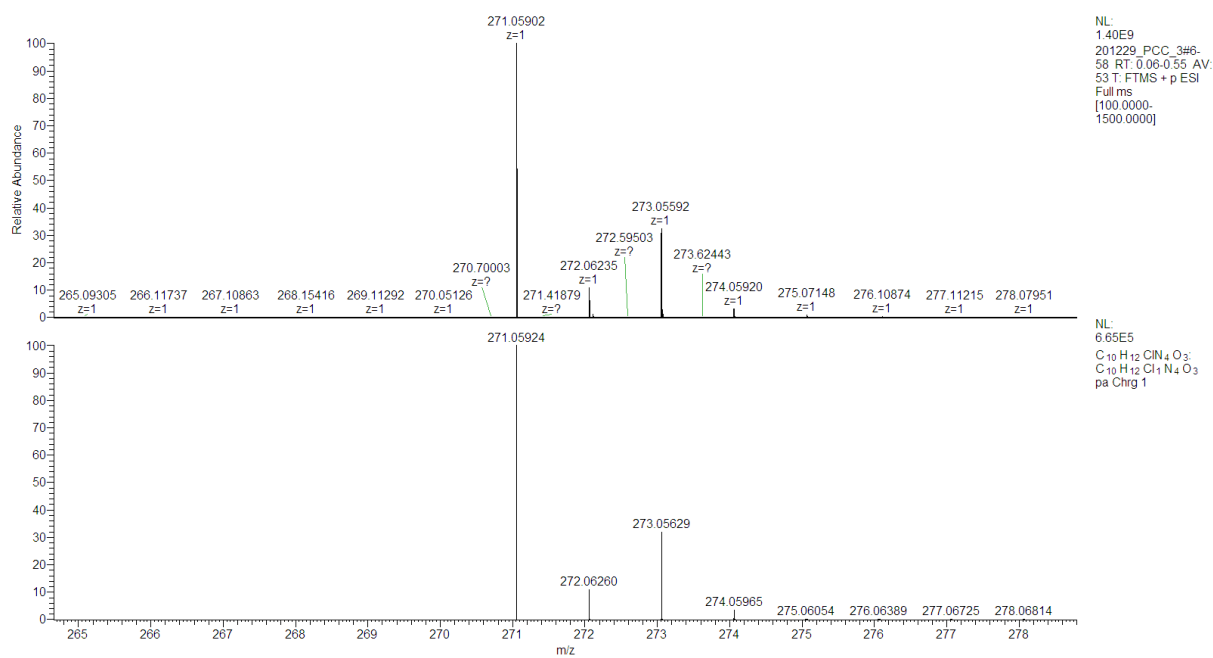
¹H NMR spectrum of **2b** (500 MHz, CDCl₃)



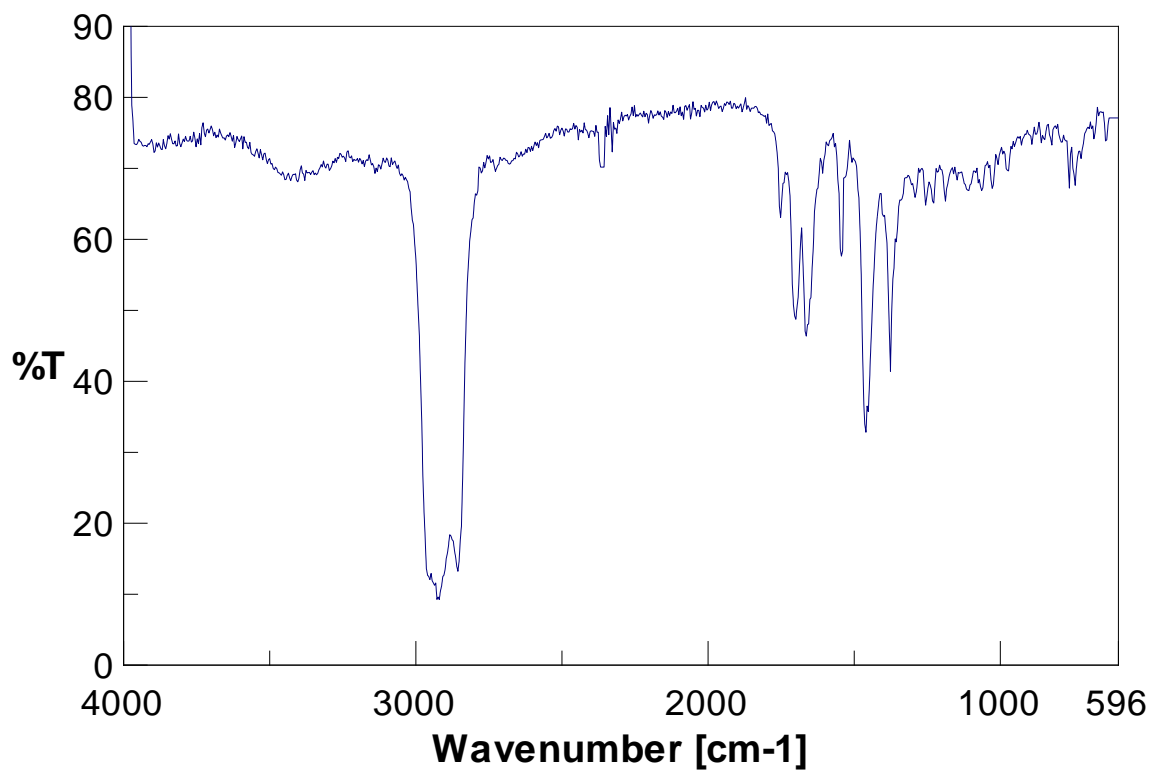
¹³C NMR spectrum of **2b** (126 MHz, CDCl₃)



FTMS spectrum of **2b** (ESI-TOF)

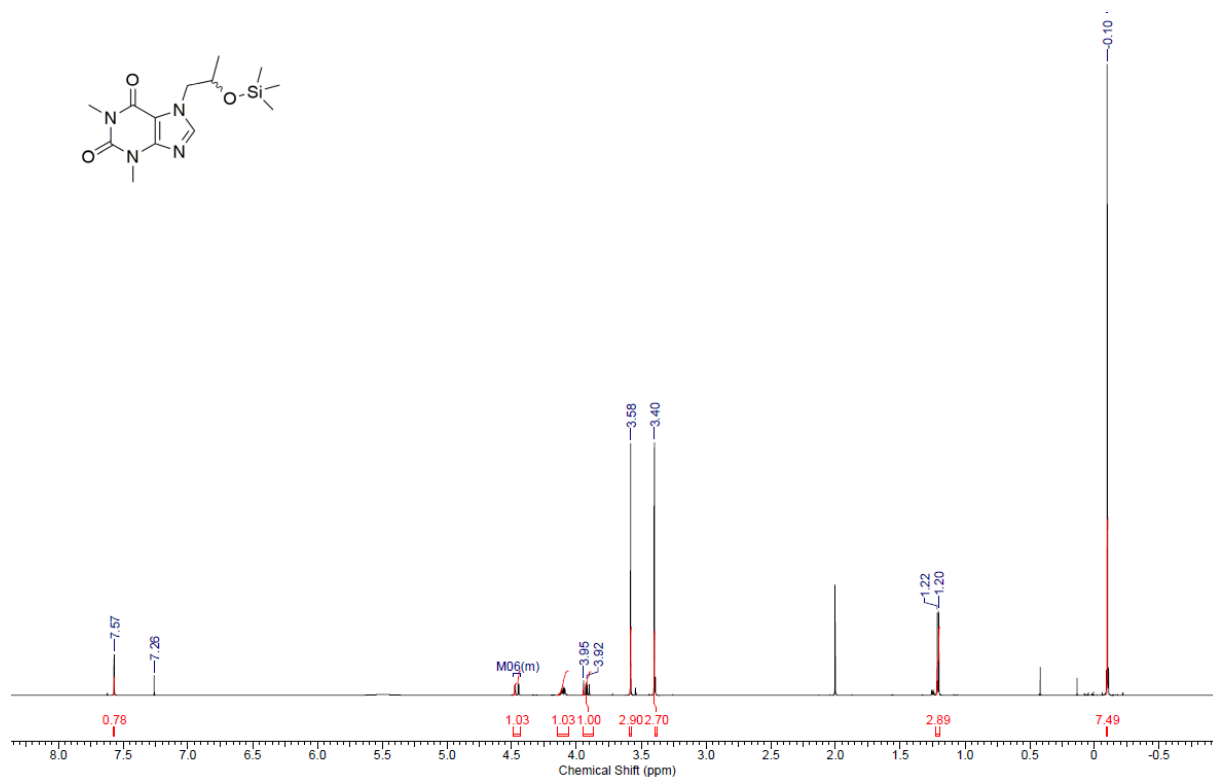


IR spectrum of **2b** (Mineral oil, Nujol)

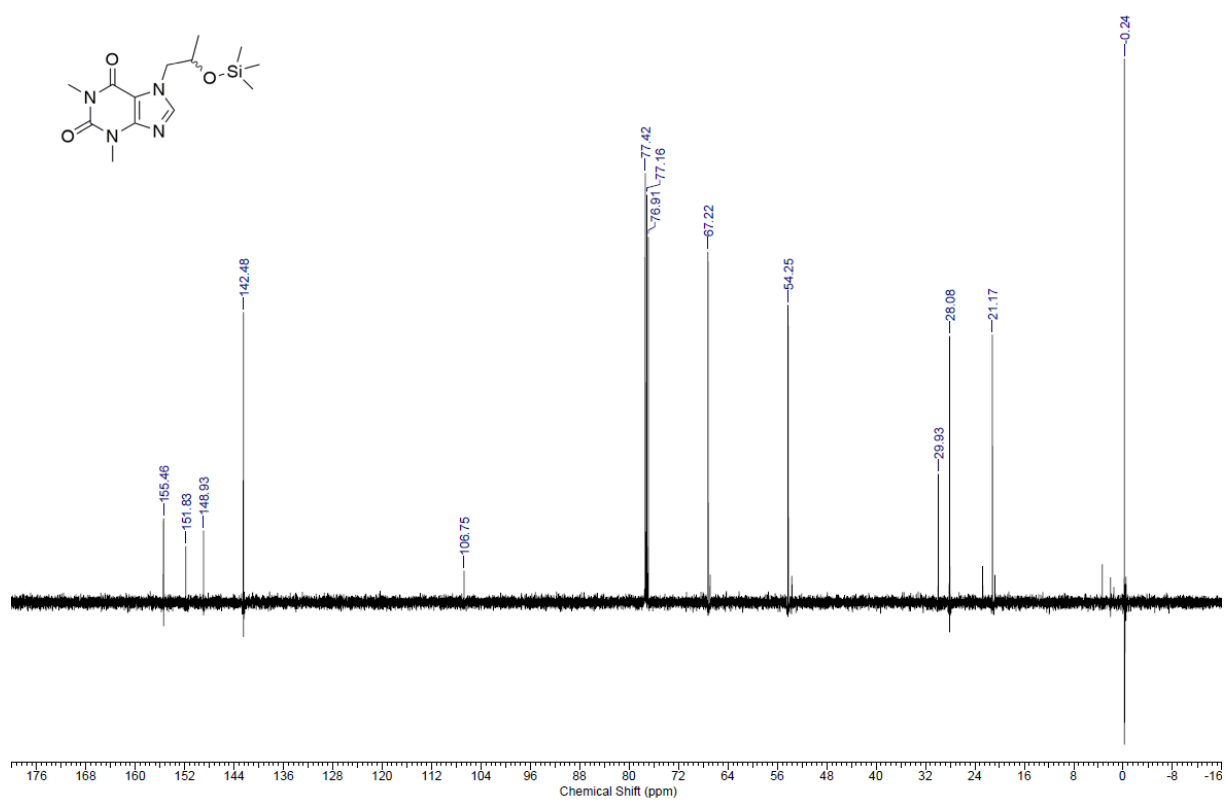


1,3-Dimethyl-7-{2-[(trimethylsilyl)oxy]propyl}-2,3,6,7-tetrahydro-1H-purine-2,6-dione (rac-3a)

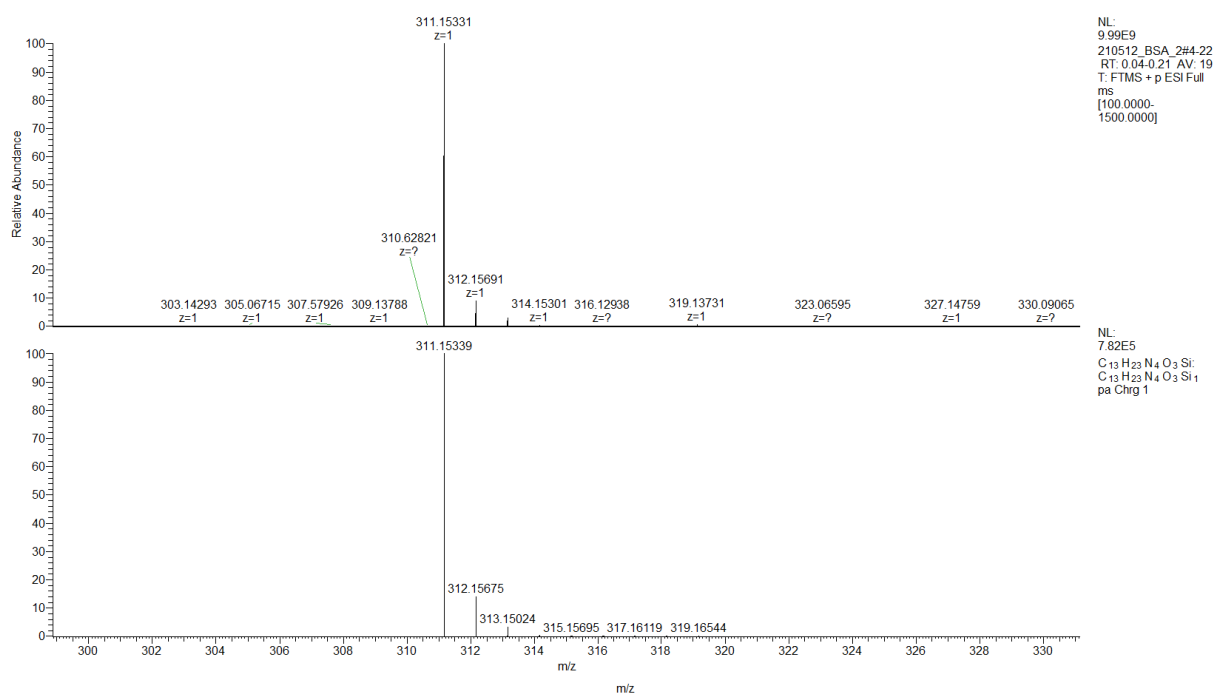
¹H NMR spectrum of *rac-3a* (500 MHz, CDCl₃)



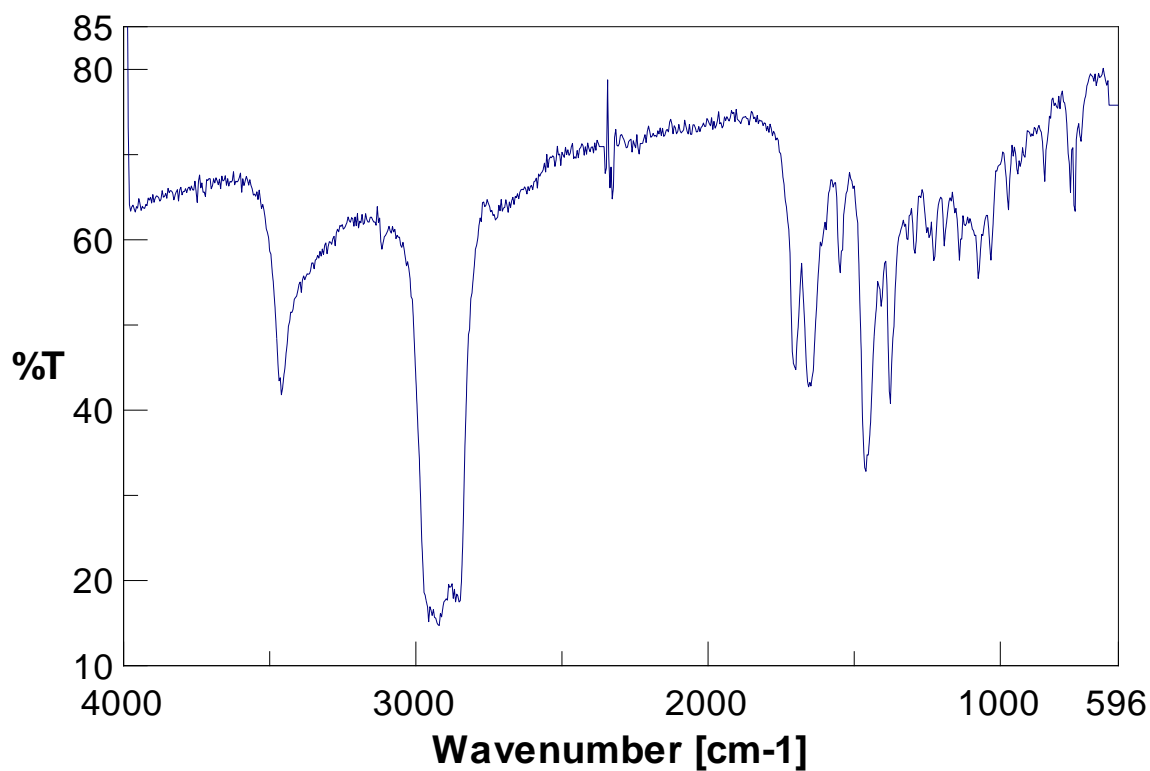
¹³C NMR spectrum of *rac-3a* (126 MHz, CDCl₃)



FTMS spectrum of *rac*-**3a** (ESI-TOF)

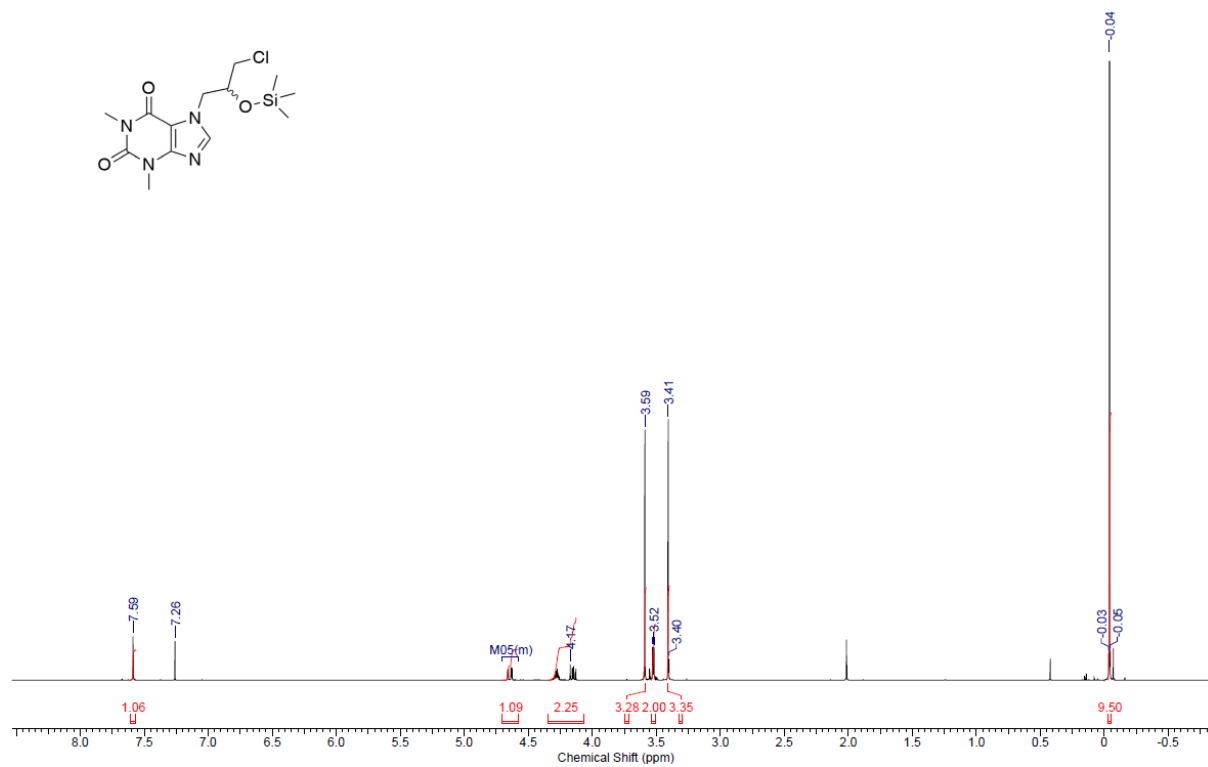


IR spectrum of *rac*-**3a** (Mineral oil, Nujol)

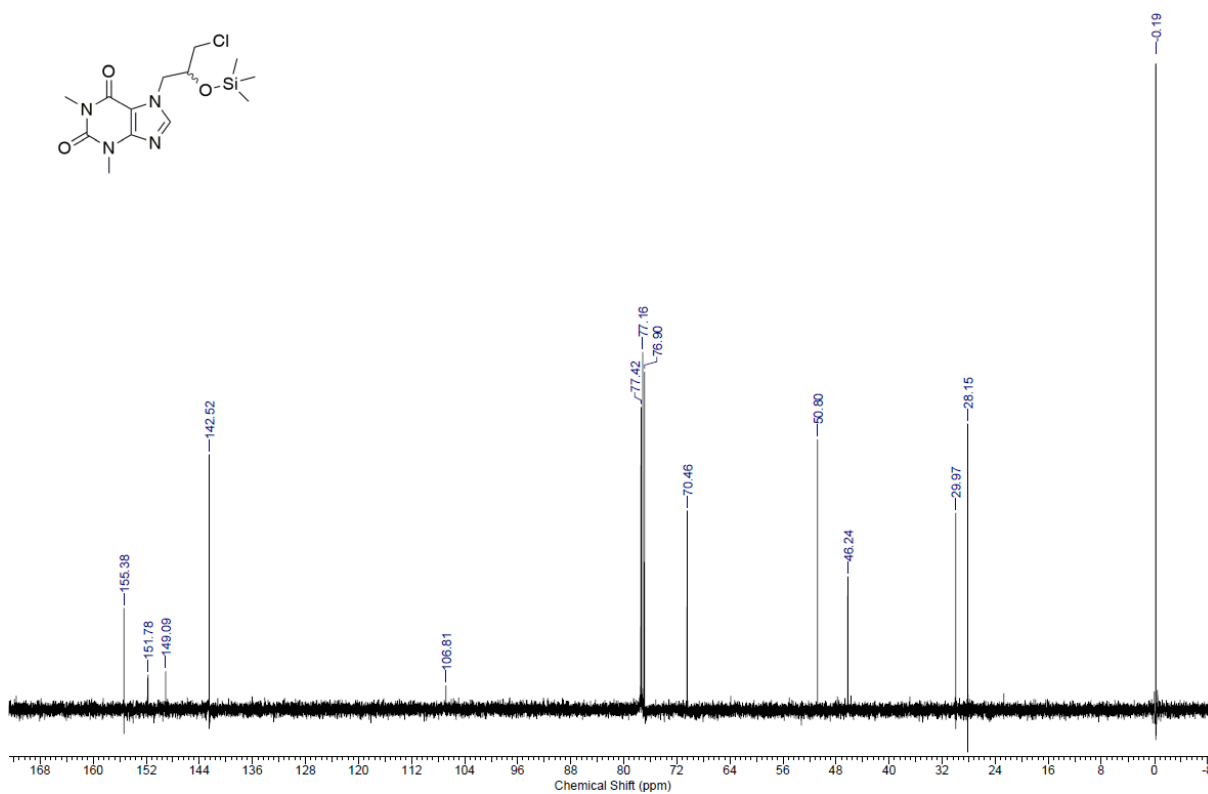


7-{3-Chloro-2-[(trimethylsilyl)oxy]propyl}-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione (*rac*-3b**)**

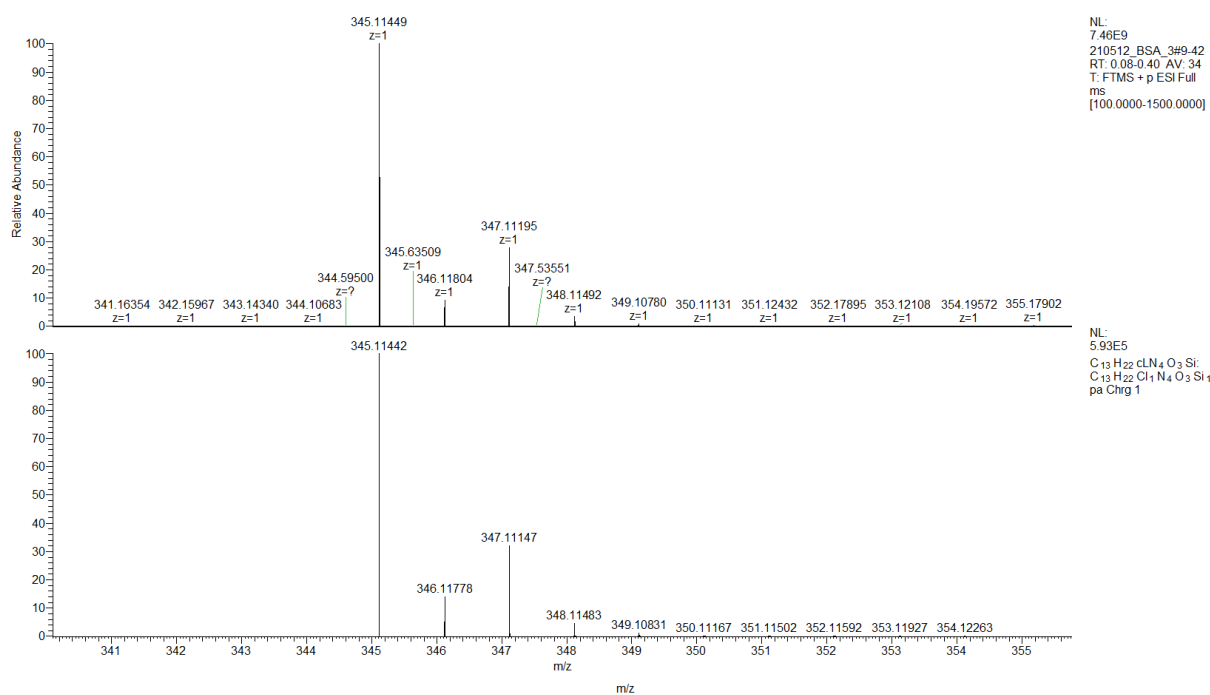
¹H NMR spectrum of *rac*-**3b** (500 MHz, CDCl₃)



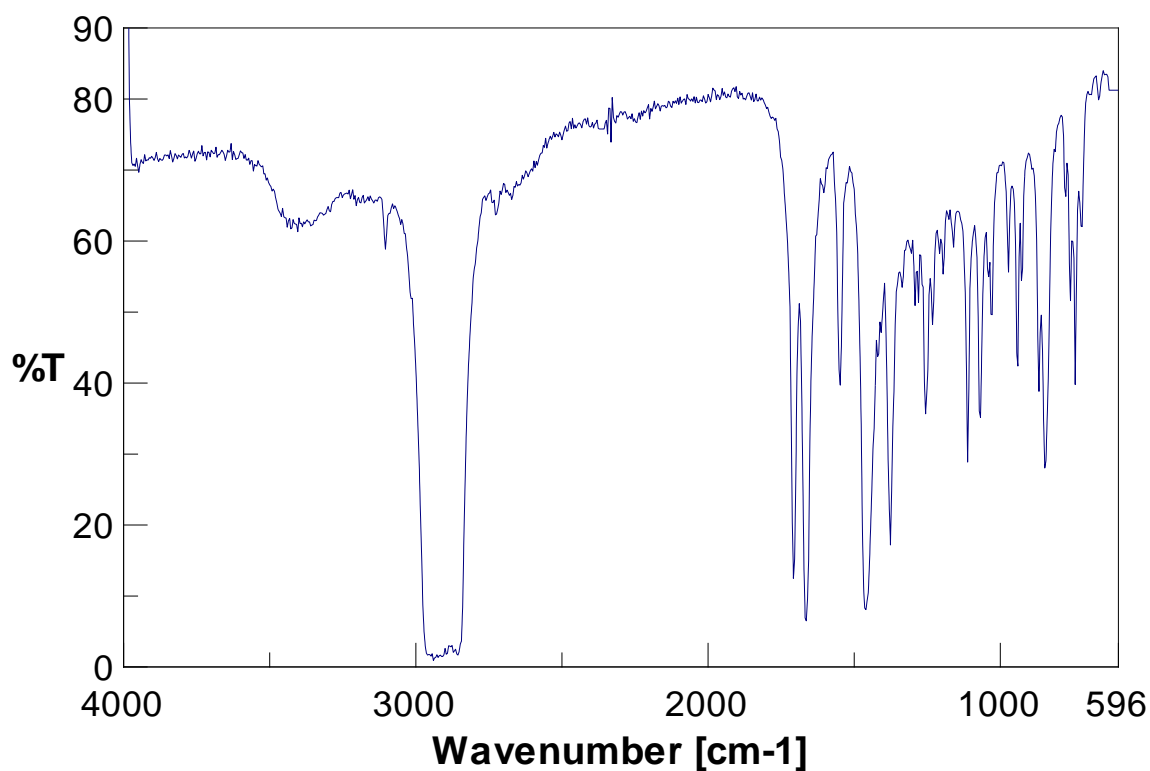
¹³C NMR spectrum of *rac*-**3b** (126 MHz, CDCl₃)



FTMS spectrum of *rac*-**3b** (ESI-TOF)

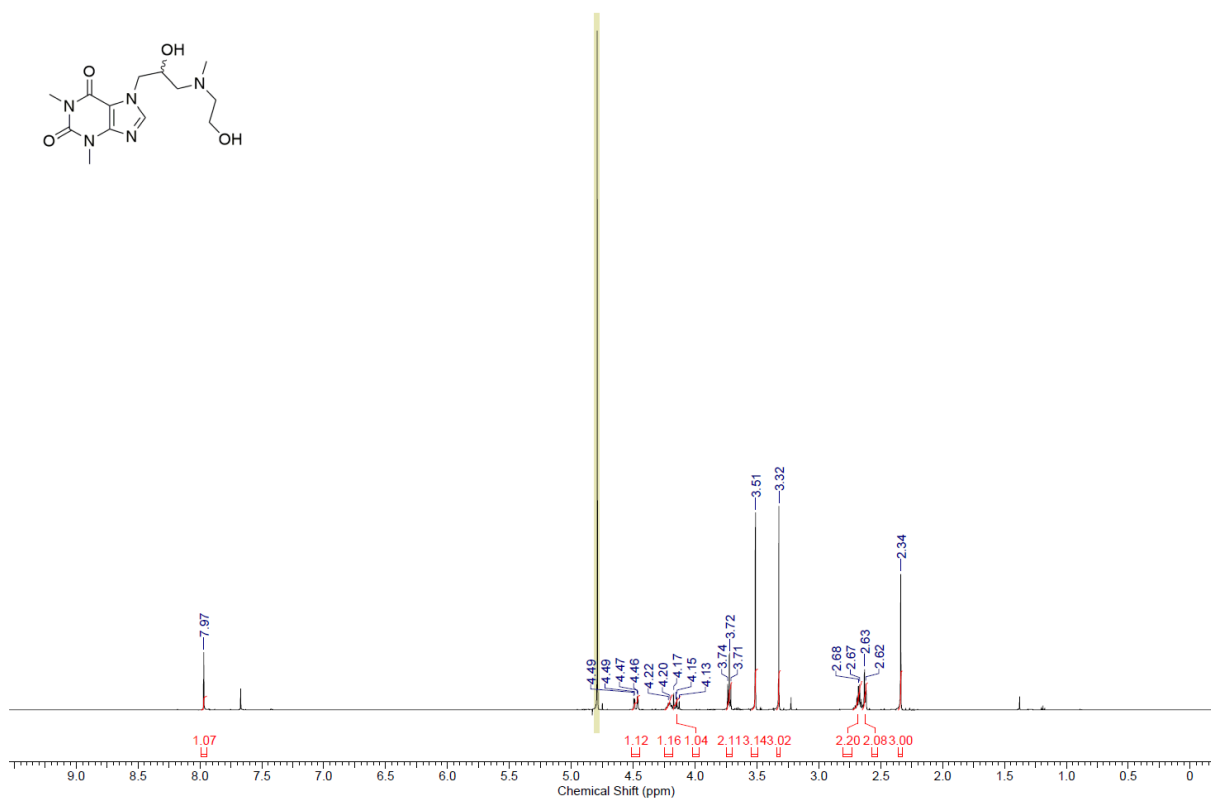


IR spectrum of *rac*-**3b** (Mineral oil, Nujol)

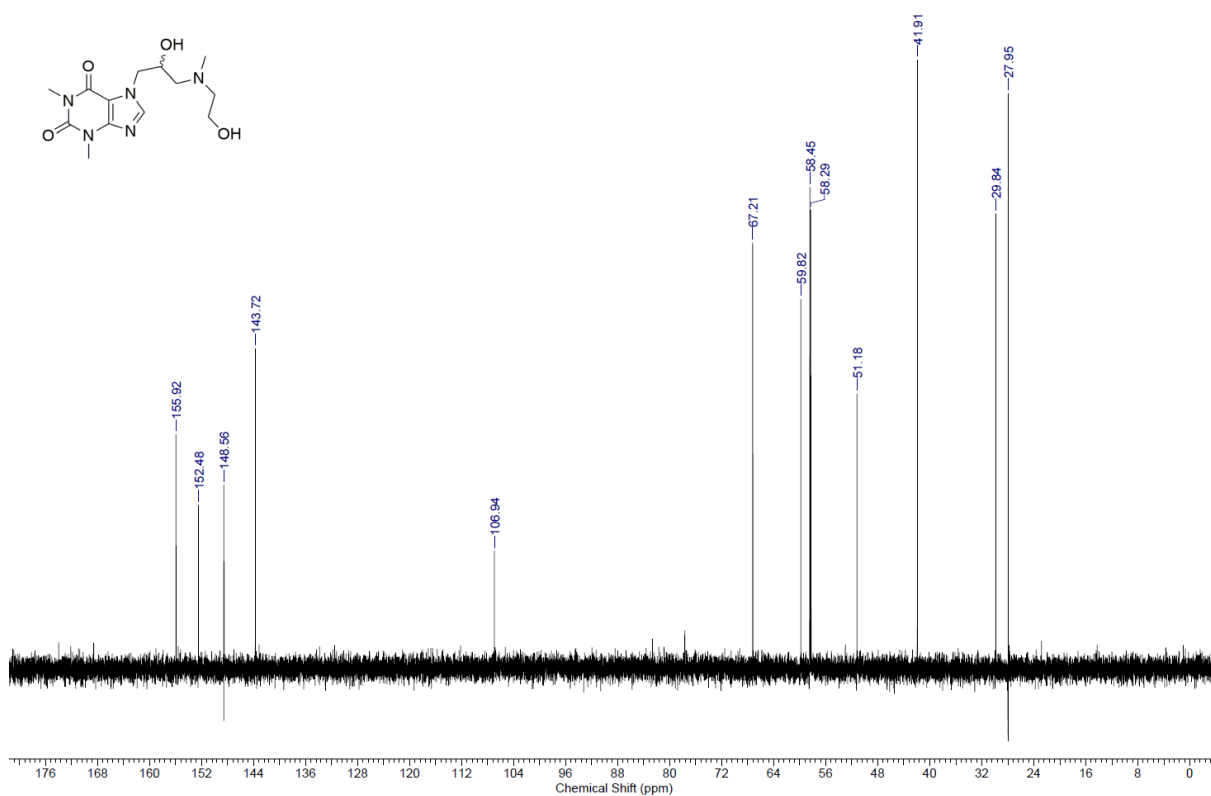


7-{2-Hydroxy-3-[(2-hydroxyethyl)(methyl)amino]propyl}-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (xanthinol, rac-4)

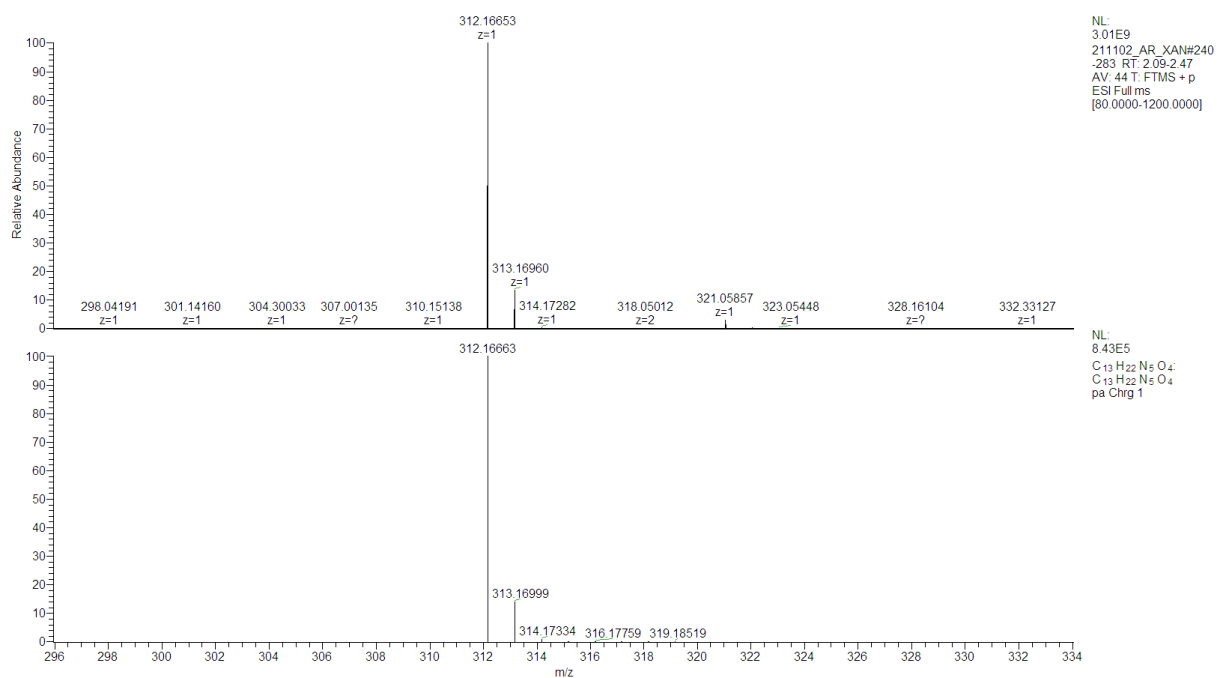
¹H NMR spectrum of *rac-4* (500 MHz, D₂O)



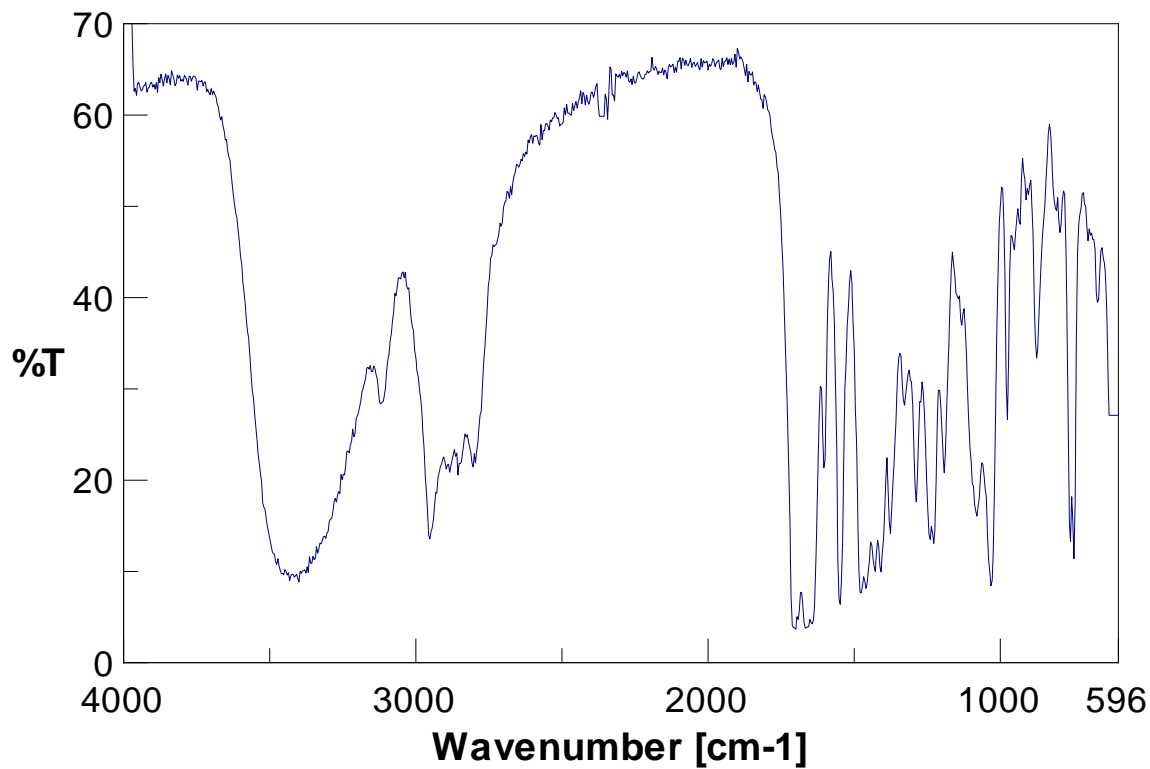
¹³C NMR spectrum of *rac-4* (126 MHz, D₂O)



FTMS spectrum of *rac-4* (ESI-TOF)

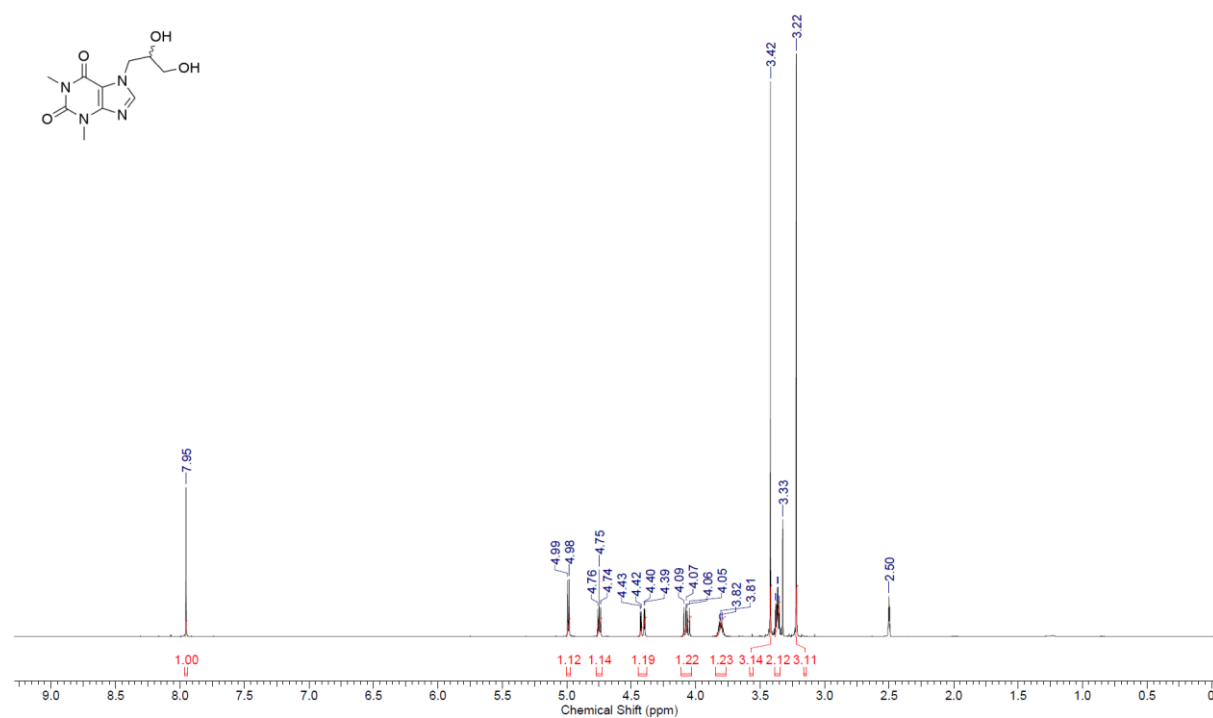


IR spectrum of *rac-4* (Mineral oil, Nujol)

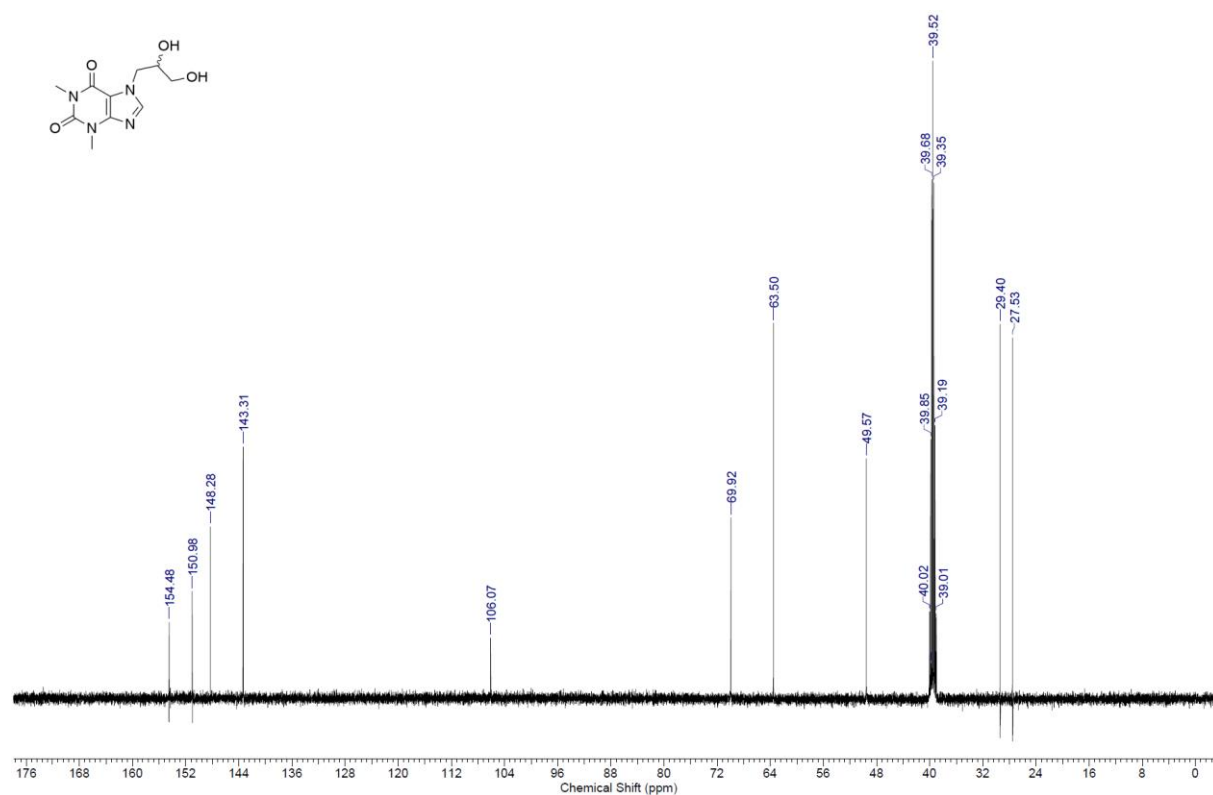


7-(2,3-Dihydroxypropyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (diprophylline, rac-5)

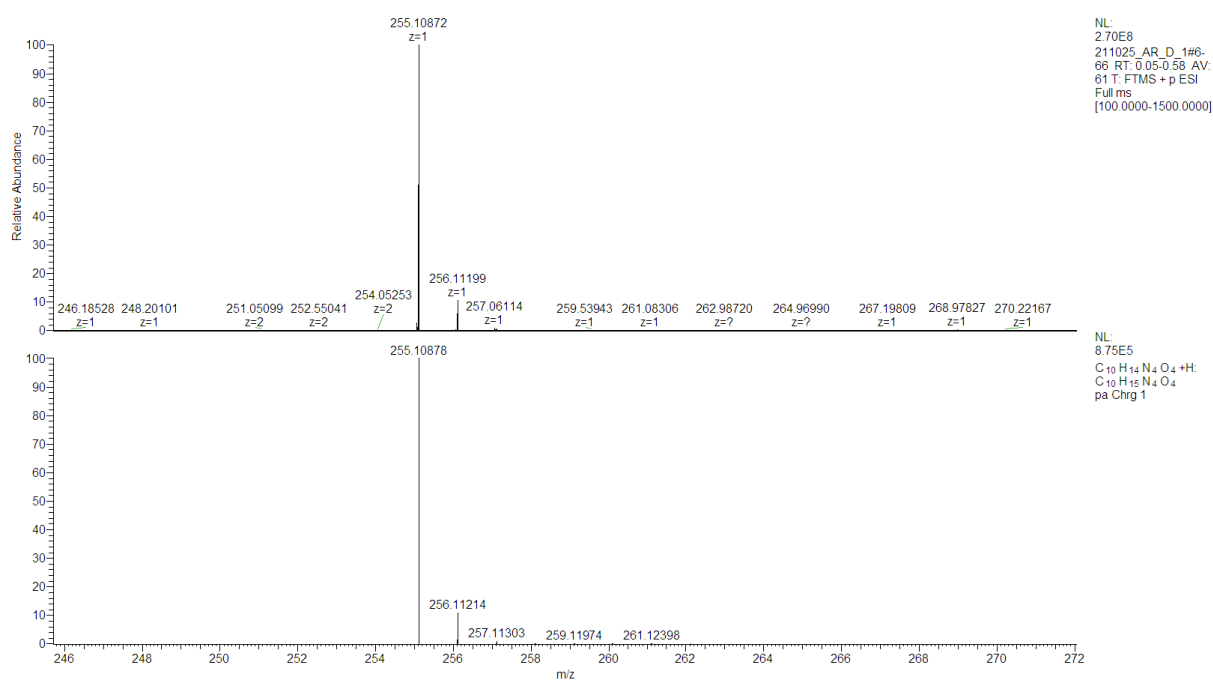
¹H NMR spectrum of *rac-5* (500 MHz, DMSO-*d*₆)



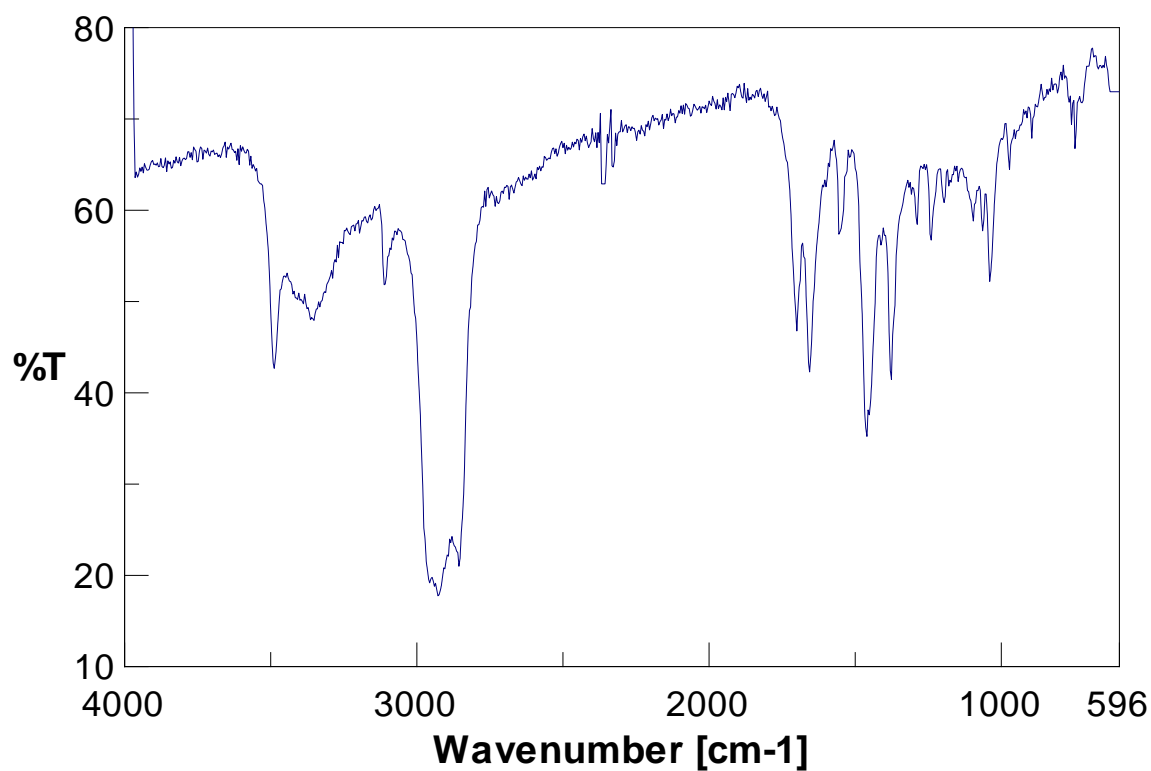
¹³C NMR spectrum of *rac-5* (126 MHz, DMSO-*d*₆)



FTMS spectrum of *rac-5* (ESI-TOF)



IR spectrum of *rac-5* (Mineral oil, Nujol)



References

- [1] Borowiecki, P.; Paprocki, D.; Dudzik, A.; Plenkiewicz, J. *J. Org. Chem.* **2016**, *81*, 380–395.
- [2] Borowiecki, P.; Młynek, M.; Dranka, M. *Bioorg. Chem.* **2021**, *106*, 104448.