Electronic Supplementary Material (ESI) for RSC Advances.

Redesigning the synthesis of Vidarabine *via* a multienzymatic reaction catalyzed by immobilized nucleoside phosphorylases

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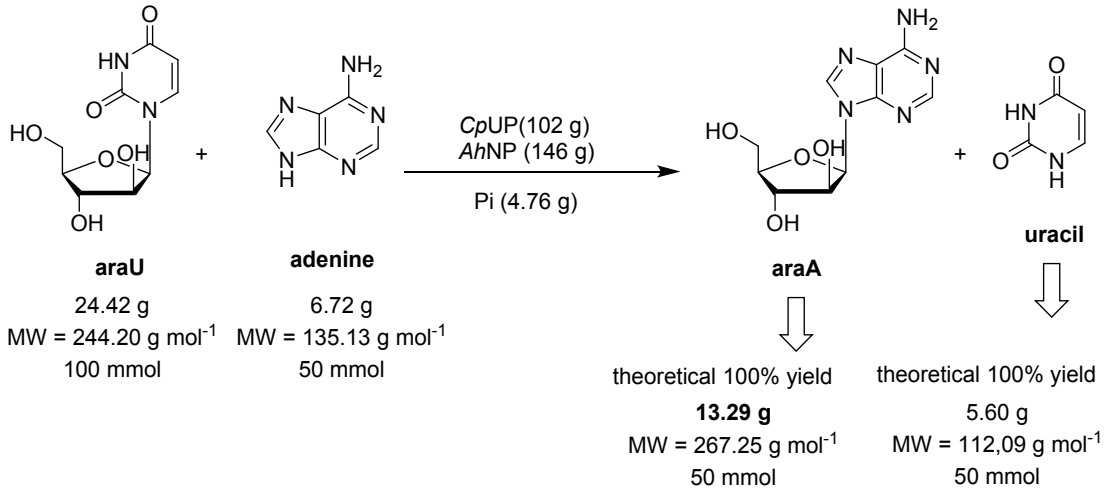
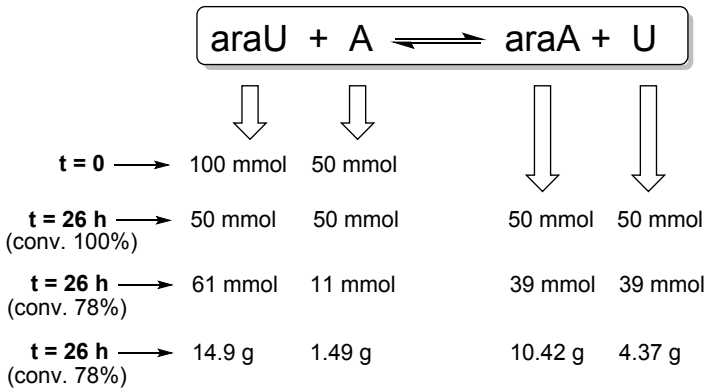
E-factor calculations

2-L scale





Final conversion: 10.42 g (78%)

Final yield: 7.04 g (53%)

Purity: 98.7 %

FINAL AMOUNT OF araA (REAL) = 6.99 g.

CALCULATIONS

As described by Maity, P.; Gopinath, C. S.; Bhaduri, S.; Lahiri, G. K. Applications of a high performance platinum nanocatalyst for the oxidation of alcohols in water. Green Chem. 2009, 11, 554-561.

1.-BASED ON ANALYTICAL YIELD (78%), WHITOUT CONSIDERING NEITHER ENZYME WASTE NOR SOLVENTS.

Total amounts of reactants: 24.42 g (araU) +6.76 g (A) = 31.18 g

Total amounts of product (araA) = 10,42 g

Amount of waste from non converted reagents: 14.9 g (araU) +1,49 g(A) = 16.39 g

Amount of waste from byproducts: 4.37 g (U) + 4.76 g (Pi) = 9,13

Total amount of waste = 16.39 +9,13 = 25.52 g

E-FACTOR: (25.52/ 10.42) = 2,45

2.-BASED ON ANALYTICAL YIELD (78%), CONSIDERING ENZYME WASTE but NOT SOLVENTS.

Total amounts of reactants: 24.42 g (araU) +6.76 g (A) = 31.18 g

Total amounts of product (araA) = 10,42 g

Amount of waste from non converted reagents: 14.9 g (araU) +1,49 g(A) = 16.39 g

Amount of waste from byproducts: 4.37 g (U) +4.76 g (Pi) +102 g (CpUP) + 146 g (AhNP) = 257,13

Total amount of waste = 16.39 +257,13 = 273.52 g

E-FACTOR: (273.52/ 10.42) = 26,25

3.-BASED ON ANALYTICAL YIELD (78%), CONSIDERING SOLVENTS

Total amounts of reactants: 24.42 g (araU) +6.76 g (A) = 31.18 g

Total amounts of product (araA) = 10,42 g

Amount of waste from non converted reagents: 14.9 g (araU) +1,49 g(A) = 16.39 g

Amount of waste from byproducts: 4.37 g (U) +4.76 g (Pi) + 2000 g (water, 2L) + 944 g (DMF, final 50%, density = 0.944) = 2,953.13

Total amount of waste = 16.39 +2,953.13= 2,969,52 g

E-FACTOR: (2,969.52/ 10.42) = 285

4.-BASED ON ANALYTICAL YIELD (78%), CONSIDERING ENZYME WASTE and SOLVENTS.

Total amounts of reactants: 24.42 g (araU) +6.76 g (A) = 31.18 g

Total amounts of product (araA) = 10,42 g

Amount of waste from non converted reagents: 14.9 g (araU) +1,49 g(A) = 16.39 g

Amount of waste from byproducts: 4.37 g (U) +4.76 g (Pi) +102 g (CpUP) + 146 g (AhNP) + 2000 g (water, 2L) + 944 g (DMF, final 50%, density = 0.944) = 3,201.13

Total amount of waste = 16.39 +3,201.13 = 3,217.52 g

E-FACTOR: (3,217.52/ 10.42) = 308,8

CALCULATIONS

1.-BASED ON FINAL YIELD (53%), WHITOUT CONSIDERING NEITHER ENZYME WASTE NOR SOLVENTS.

Total amounts of reactants: 24.42 g (araU) +6.76 g (A) = 31.18 g

Total amounts of product (araA) = 6,99 g

Amount of waste from non converted reagents: 14.9 g (araU) +1,49 g(A) = 16.39 g

Amount of waste from byproducts: 4.37 g (U) + 4.76 g (Pi) = 9,13

Total amount of waste = 16.39 +9,13 = 25.52 g

E-FACTOR: (25.52/ 6.99) = 3.65

2.-BASED ON FINAL YIELD (53%), CONSIDERING ENZYME WASTE but NOT SOLVENTS.

Total amounts of reactants: 24.42 g (araU) +6.76 g (A) = 31.18 g

Total amounts of product (araA) = 6.99 g

Amount of waste from non converted reagents: 14.9 g (araU) +1,49 g(A) = 16.39 g

Amount of waste from byproducts: 4.37 g (U) +4.76 g (Pi) +102 g (CpUP) + 146 g (AhNP) = 257,13

Total amount of waste = 16.39 +257.13 = 273.52 g

E-FACTOR: (273.52/ 6.99) = 39.13

3.-BASED ON FINAL YIELD (53%), CONSIDERING SOLVENTS

Total amounts of reactants: 24.42 g (araU) +6.76 g (A) = 31.18 g

Total amounts of product (araA) = 6.99 g

Amount of waste from non converted reagents: 14.9 g (araU) +1,49 g(A) = 16.39 g

Amount of waste from byproducts: 4.37 g (U) +4.76 g (Pi) + 2000 g (water, 2L) + 944 g (DMF, final 50%, density = 0.944) = 2,953.13

Total amount of waste = 16.39 +2,953.13= 2,969,52 g

E-FACTOR: (2,969.52/ 6.99) = 424.8

4.-BASED ON FINAL YIELD (53%), CONSIDERING ENZYME WASTE and SOLVENTS.

Total amounts of reactants: 24.42 g (araU) +6.76 g (A) = 31.18 g

Total amounts of product (araA) = 10,42 g

Amount of waste from non converted reagents: 14.9 g (araU) +1,49 g(A) = 16.39 g

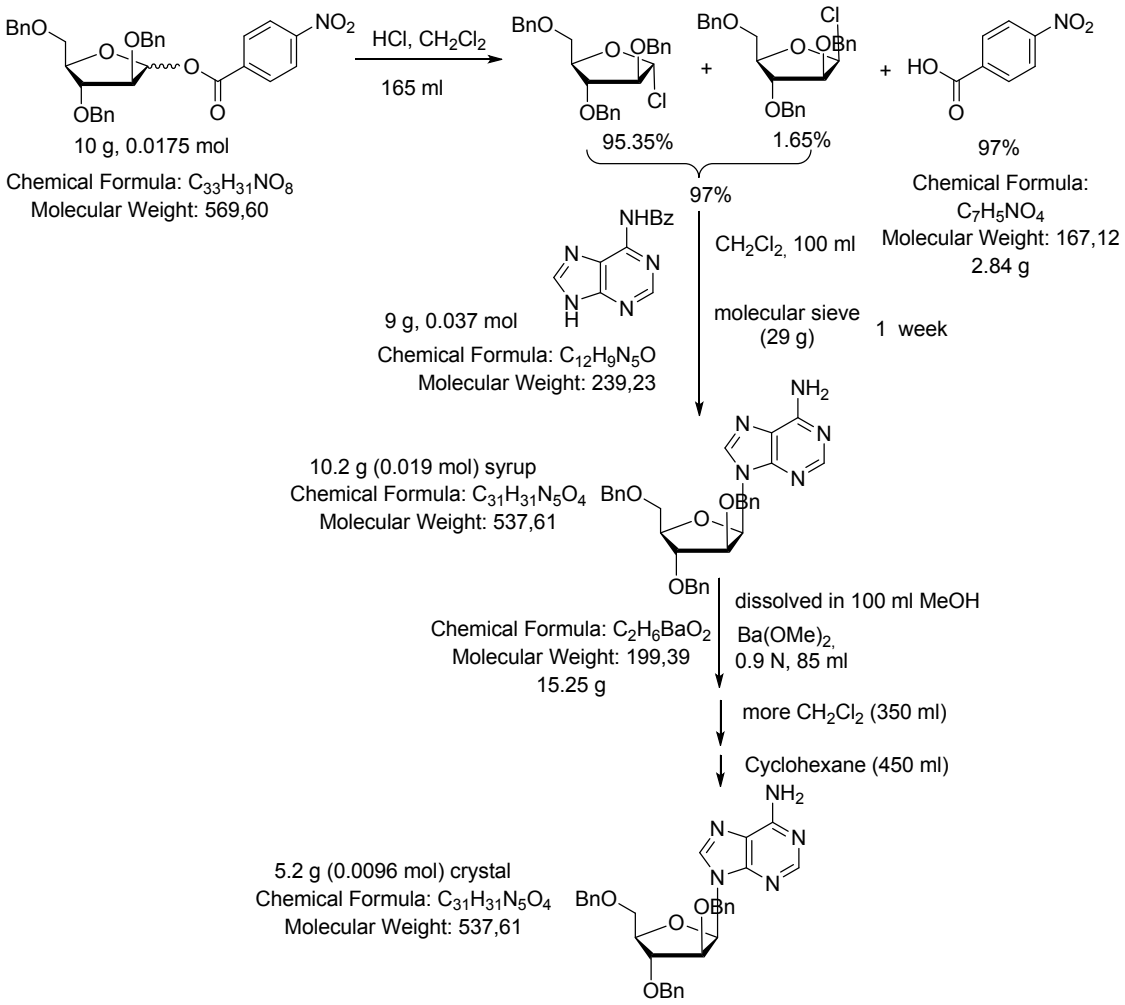
Amount of waste from byproducts: 4.37 g (U) +4.76 g (Pi) +102 g (CpUP) + 146 g (AhNP) + 2000 g (water, 2L) + 944 g (DMF, final 50%, density = 0.944) = 3,201.13

Total amount of waste = 16.39 +3,201.13 = 3,217.52 g

E-FACTOR: (3,217.52/ 6.99) = 460.3

CHEMICAL SYNTHESIS, according to Glaudemans, C. P. J.; Fletcher, J. Journal of Organic Chemistry 1963, 28, 3004–3006.

1.-FIRST STEP



1.1.-WHITOUT CONSIDERING SOLVENTS.

Total amounts of reactants: 10 g (2,3 5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-*D*-arabinofuranose) +9 g (*N*-benzoyladenine) + 0.62 g HCl (estimated, from 97% yield of theoretical 0.0175 mol) += 19.62 g

Total amounts of product (9-(2,3,5-Tri-*O*-benzyl-(*β*-*D*-arabinofuranosyl)adenine) = 5,2 g

Amount of waste:

- non converted reagents: 0.3 g (non converted substrate)

- 2.84 g (p-nitrobenzoic acid)
- 29 g (molecular sieve, not considered)
- 15.25 g ($Ba(OMe)_2$)

Total amount of waste = 0.3 + 2.84 + 15.25 = 18.39 g

E-FACTOR: (18.39/ 5.2) = 3.5

1.2.-CONSIDERING SOLVENTS.

Total amounts of reactants: 10 g (2,3 5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-*D*-arabinofuranose) +9 g (*N*-benzoyladenine) + 0.62 g HCl (estimated, from 97% yield of theoretical 0.0175 mol) += 19.62 g

Total amounts of product (9-(2,3,5-Tri-*O*-benzyl-(*β*-*D*-arabinofuranosyl)adenine) = 5,2 g

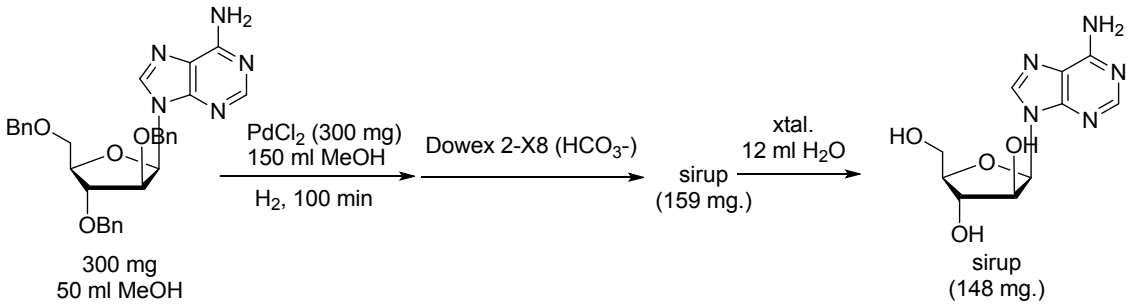
Amount of waste:

- non converted reagents: 0.3 g (non converted substrate)
- 2.84 g (p-nitrobenzoic acid)
- 29 g (molecular sieve, not considered)
- 15.25 g ($Ba(OMe)_2$)
- SOLVENTS:
  - CH_2Cl_2 = 515 ml x 1.33 g/ml = 685 g
  - C_6H_{12} = 450 ml x 0.78 g/ml = 351g

Total amount of waste = 0.3 + 2.84 + 15.25 + 685 + 351 = 1, 046.5 g

E-FACTOR: (1,046.5/ 5.2) = 201.2

2.-SECOND STEP



2.1.-WHITOUT CONSIDERING SOLVENTS.

Total amounts of reactants: 0.3 g (9-(2,3,5-tri-O-benzyl β-*D*-arabinofuranosyl)adenine) + 0.3 g $PdCl_2$ = 0.6 g

Total amounts of product (9-(β-*D*-arabinofuranosyl)adenine) = 0.148 g

Amount of waste: 0.6-0.148 = 0.452

E-FACTOR: (0.452/ 0.148) = 3.05

2.2.- CONSIDERING SOLVENTS

Total amounts of reactants: 0.3 g (9-(2,3,5-tri-O-benzyl β-*D*-arabinofuranosyl)adenine) + 0.3 g $PdCl_2$ = 0.6 g

Total amounts of product (9-(β-*D*-arabinofuranosyl)adenine) = 0.148 g

Amount of waste:

- SOLVENTS:
  - CH_3OH = 200 ml x 0.7918 g/ml = 158.4 g
  - H_2O = 12 ml x 1 g/ml = 12g

(0.6-0.148 = 0.452)+158.4+12 =171 g

E-FACTOR: (171/ 0.148) = 1155

3.- OVERALL DATA: Considering both steps

3.1.- WITHOUT CONSIDERING SOLVENTS

Mean value: (2 +3.05)/2 = 2.5

3.2.- CONSIDERING SOLVENTS

Mean value: (201,2 +1155)/2 = 678

Figure S1 Chromatogram of the purified araA (from 2 L reaction, see Table 5).

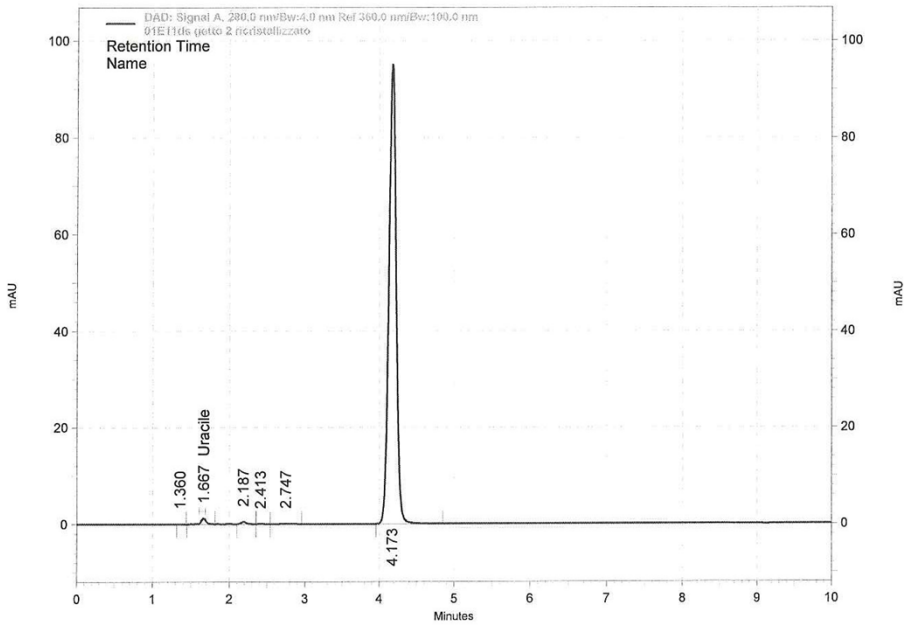
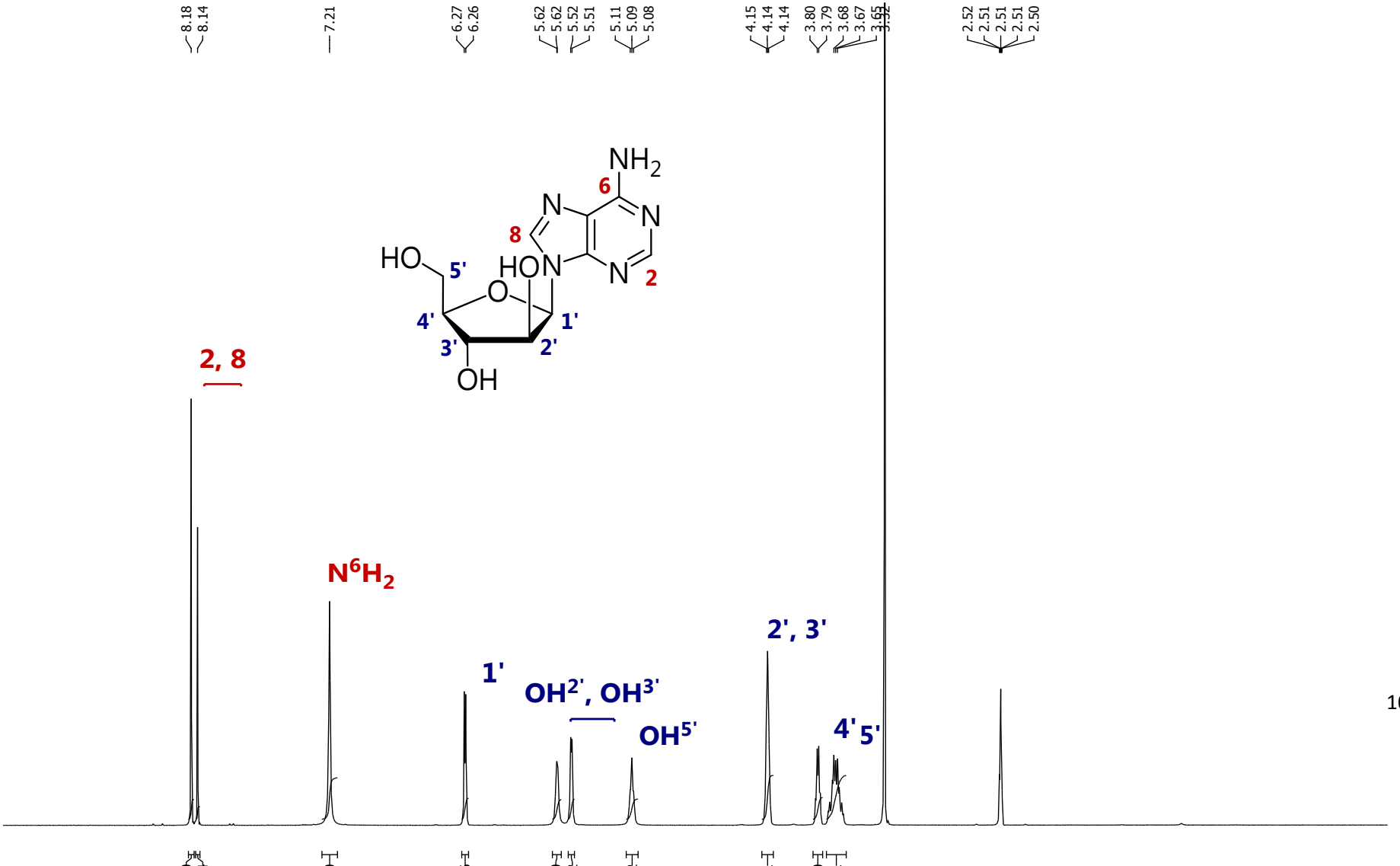
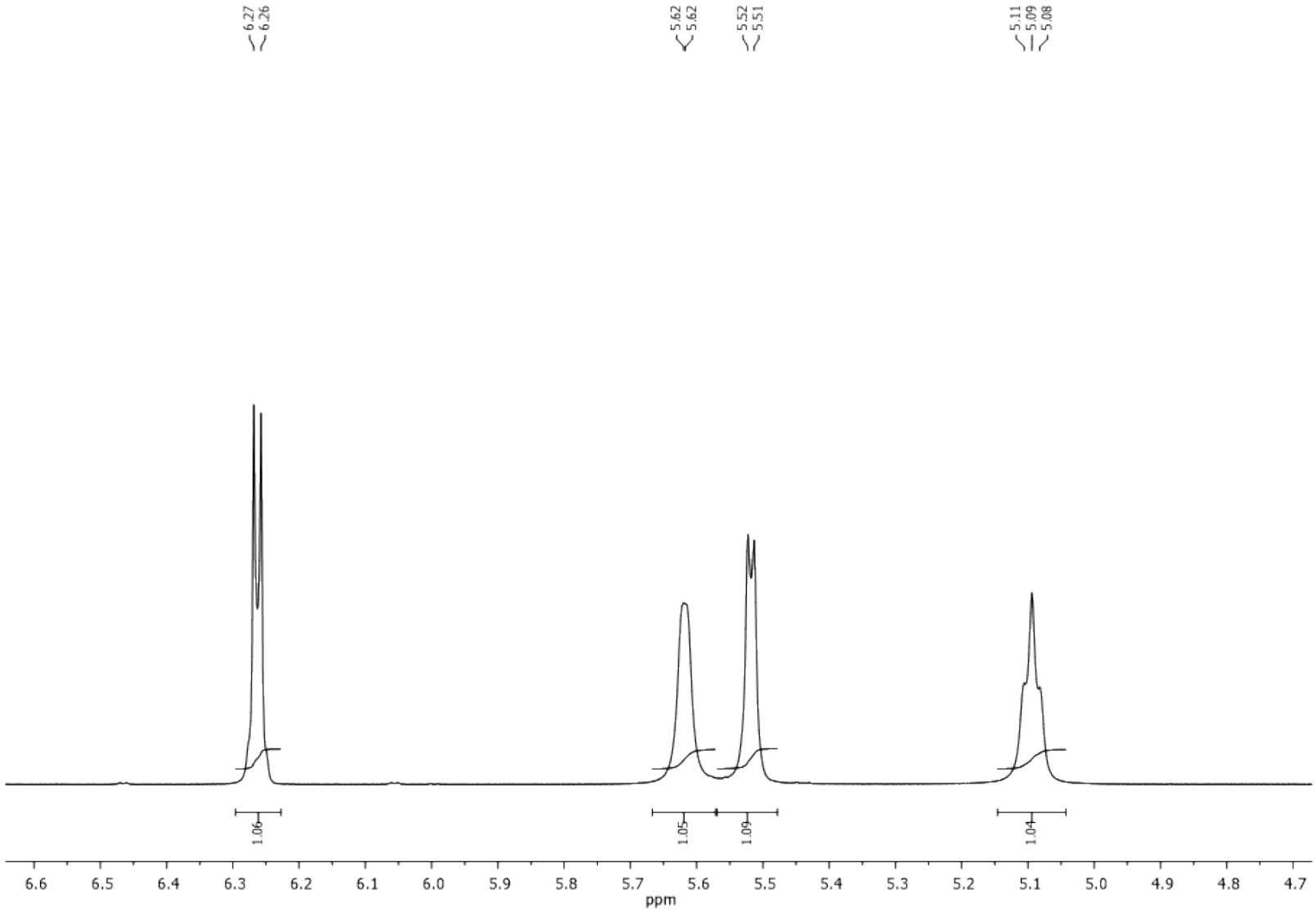


Figure S2 ^{1}H NMR spectrum of the purified araA (from 2 L reaction, see Table 5).

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6.26
5.62
5.62
5.52
5.51
5.11
5.09
5.08
1.06
1.05
1.09
1.04
6.6
6.5
6.4
6.3
6.2
6.1
6.0
5.9
5.8
5.7
5.6
5.5
5.4
5.3
5.2
5.1
5.0
4.9
4.8
4.7
ppm

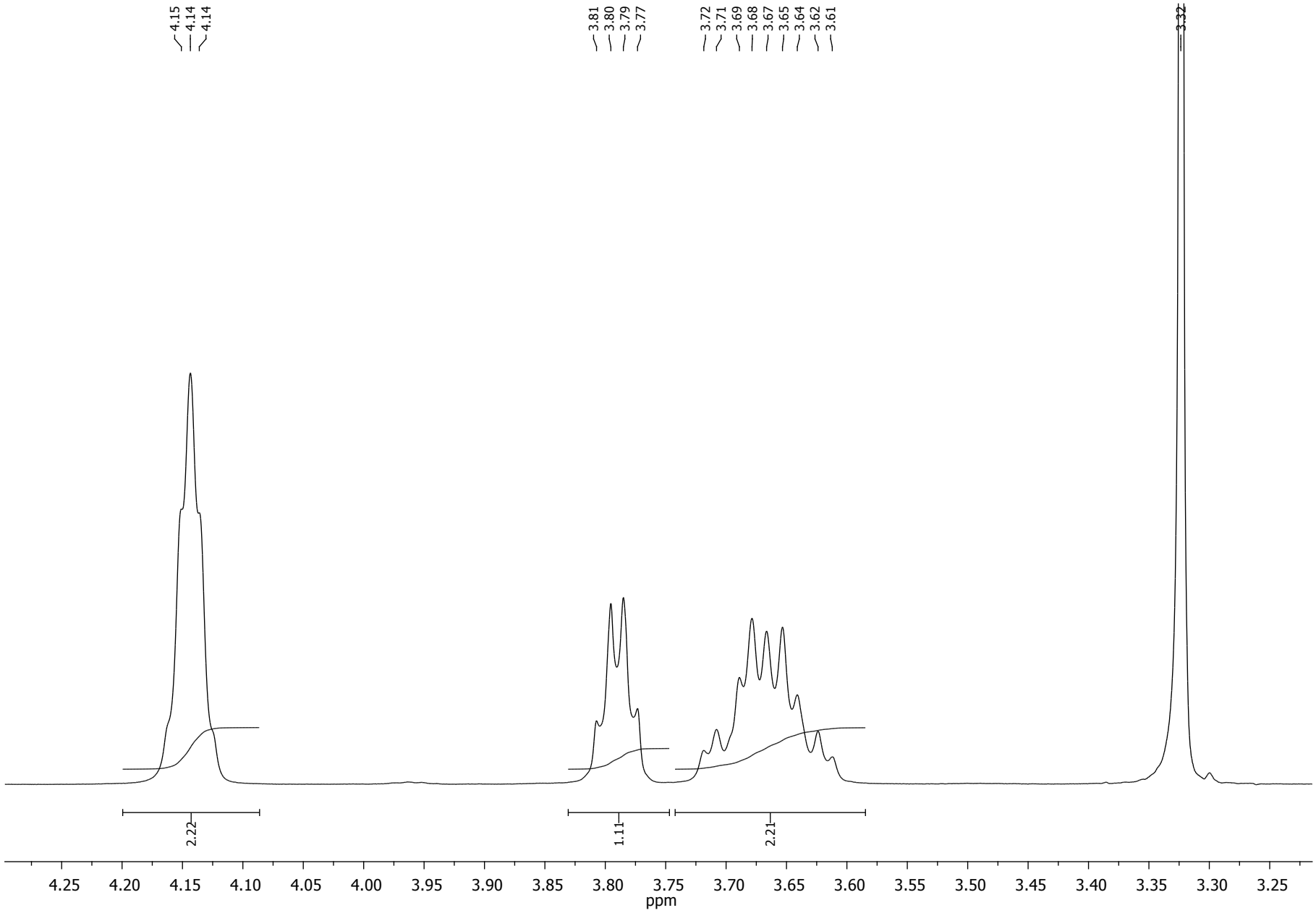
4.15
4.14
4.14
3.81
3.80
3.79
3.77
3.72
3.71
3.69
3.68
3.67
3.65
3.64
3.62
3.61
3.32
2.22
1.11
2.21
4.25
4.20
4.15
4.10
4.05
4.00
3.95
3.90
3.85
3.80
3.75
3.70
3.65
3.60
3.55
3.50
3.45
3.40
3.35
3.30
3.25
ppm

Figure S3 ESI-Q-Tof-MS spectrum of the purified araA (from 2 L reaction, see Table 5).