Supporting Information

Glucose promoted facile reduction of azides to amines in aqueous alkaline conditions

Nisha Chandna, Fatehjeet Kaur, Shobhna Kumar and Nidhi Jain*

Department of Chemistry, Indian Institute of Technology, New Delhi-110016

*E-mail: njain@chemistry.iitd.ac.in; Fax: +91 11 26581102; Tel: +91 11 26591562

EXPERIMENTAL:

General Information:

All reactions were carried out under an air atmosphere in oven-dried microwave tube or sealed tube. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on a 0.25 mm silica gel plates (60F–254) and visualized under UV illumination at 254 nm and iodine chamber. Further visualization was achieved by iodine vapour adsorbed on silica gel depending on the product type. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Column chromatography was performed on silica gel 100–200 mesh using a mixture of hexane and ethyl acetate as eluent, an isolated compounds were characterized by ^{1}H NMR, $^{13}C\{1H\}$ NMR, and HRMS data. NMR spectra for all the samples were taken in deuterochloroform ($CDCl_3$) and dimethylsufoxide-d_6 (DMSO-d_6) as the solvents. ^{1}H and ^{13}C-NMR spectra were recorded at ambient temperature on 400MHz/300 MHz and 75 MHz spectrometer using tetramethylsilane (TMS) as internal reference. The chemical shifts are quoted in δ units, parts per million (ppm) up field from the signal of internal TMS. ^{1}H NMR data is represented as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet), integration and coupling constant(s) *J* in Hertz (Hz). High resolution mass spectra (HRMS) were recorded on a Bruker MicroTOF-QII mass spectrometer using electrospray ionization-time of flight (ESI-TOF) reflectron experiments with positive ion polarity. The source had end plate offset (-500 to 128 nA), capillary (-4500 to 2512 nA), nebulizer (0.3 bar), dry gas (4.0 L/min) and dry temperature (180 °C).

Reagent Information:

All reagents were weighed and handled in air at room temperature. All the solvents were bought from Aldrich, Spectrochem and were used as received. For column chromatography, silica gel (100–200 mesh), and (230-400) from SRL Co. was used. A gradient elution using ethyl acetate-hexane was performed, based on Merck aluminium TLC sheets (silica gel 60F 254). Various anilines and sulphonyl chlorides were bought from Spectrochem, Sigma Aldrich and Merck.

Procedure for the synthesis of aromatic azides:

The desired aniline (1.0 equiv.) was suspended in water; concentrated aqueous HCl was added (10% v/v) and the contents were cooled at 0 °C. A solution of $NaNO_2$ (1.2 equiv.) in water was added drop wise at 0 °C and the mixture was stirred for 20 min. A solution of NaN_3 (1.5 equiv.) in water was added drop wise at 0 °C and the obtained suspension was stirred for 3 hrs. The solution was extracted with diethylether; the organic phase was washed with brine (saturated solution), dried over $MgSO_4$, filtered and then concentrated under reduced pressure to afford the desired azido-benzene derivatives.

Procedure for the synthesis of sulphonyl azides:

A solution of sodium azide (39.3 mmol, 1.5 equiv.) in water (15 mL) was added drop wise over 1 h to a solution of sulphonyl chloride (26.2 mmol, 1.0 equiv.) in acetone (50 mL) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. After completion of reaction (monitored by TLC) acetone was removed under reduced pressure and the reaction mixture was extracted with ether (2 x 40 mL). The combined ether layers were washed with 5% Na_2CO_3 (2 x 20 mL) and water (2 x 20 mL), dried over Na_2SO_4 evaporated under reduced pressure to obtain the desired sulphonyl azides which were used for the reduction reaction without further purification.

General procedure for the synthesis of compounds (2a-2x):

To a mixture of azide/sulphonyl azide **1** (1 mmol, 1 equiv.), D-Glucose (2 mmol) and KOH (3 mmol), water (100 µL) was added. The reaction mixture was heated in a sealed tube or microwave tube covered with septum at 85 °C until completion, as monitored by TLC. The contents were cooled, and aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure. Most of the amines obtained by this method were analytically pure, and required no further purification by column chromatography. For getting an ultrapure sample, and in case of large scale reaction, the residue was purified over a column of silica gel using ethyl acetate, hexane eluent to give the desired product. Synthesized products were confirmed by ^{1}H NMR and ^{13}C NMR.

Procedure for the reduction of 1y to obtain 2y:

To a mixture of 5-(azidomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one **1y** (1 mmol, 1 equiv.), D-Glucose (3 mmol) and K_2CO_3 (6 mmol), water (100 µL) was added. The

reaction mixture was heated in a sealed tube at 85 °C till 7 h and monitored by TLC. The reaction was cooled and aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified over a column of silica gel using DCM and methanol to give the desired product. **2y** was confirmed by ^1H NMR and ^{13}C NMR.

Control experiment in D_2O:

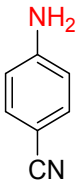
To a mixture of azide **1a** (1 mmol, 1 equiv.), D-Glucose (2 mmol) and KOH (3 mmol), D_2O (100 µL) was added. The reaction mixture was heated in a sealed tube at 85 °C until completion, as monitored by TLC. The reaction was cooled and aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified over a column of silica gel using ethyl acetate, hexane eluent to give the desired product.

NMR study for the alkaline degradation of glucose in the reaction: D-Glucose (2 mmol) was added to the mixture of azide **1a** (1 mmol) and KOH (3 mmol) in D_2O (100 µL) and reaction mixture was heated in a sealed tube at 85 °C until completion. After completion of the reaction, the reaction vessel was kept at room temperature and cooled. The contents were dissolved in DMSO-d_6, and ^1H and ^{13}CNMR of this sample was acquired.

Analytic data of compounds 2a-2y:

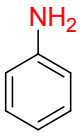
All compounds were identified by comparison of spectral data with literature.[1-4]

4-aminobenzonitrile (2a)



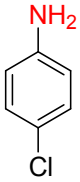
Yield 99% (117.2 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (d, J_1 = 9, 2H), 6.66 (d, J_1 = 9, 2H), 4.21 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.5, 133.8, 120.2, 114.5, 100.1.

Aniline (2b)



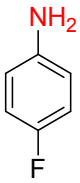
Yield 95% (88.4 mg); ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.25-7.19 (m, 2H), 6.85-6.80 (m, 1H), 6.69 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 129.7, 118.6, 115.5.

4-chloroaniline (2c)



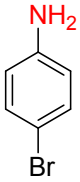
Yield 96% (121.9 mg); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.02 (d, J_1 = 8.4, 2H), 6.58 (d, J_1 = 8.1, 2H), 5.20 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 148.2, 128.6, 119.9, 115.6.

4-fluoroaniline (2d)



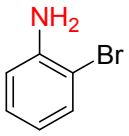
Yield 97% (107.7 mg); ^{1}H NMR (300 MHz, $CDCl_3$): 6.88-6.80 (m, 2H), 6.63-6.57 (m, 2H), 3.53 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 156.4 (d, $^1J_{CF}$ = 234 Hz), 142.6, 116.1 (d, $^3J_{CF}$ = 7.5 Hz), 115.7 (d, $^2J_{CF}$ = 22.3 Hz).

4-bromoaniline (2e)



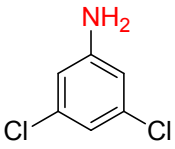
Yield 94% (160.7 mg) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, J_1 = 7.5, 2H), 7.26 (d, J_1 = 7.5, 2H), 3.57 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 148.43, 131.79, 116.32, 106.66.

2-bromoaniline (2f)



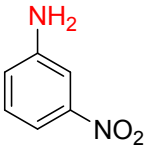
Yield 85% (145.3 mg) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (dd, J_1 = 7.5, J_2 = 3, 1H), 7.06-7.11 (m, 1H), 6.73 (dd, J_1 = 7.5, J_2 = 3, 1H), 6.63-6.57 (m, 1H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.1, 132.6, 128.4, 119.4, 115.8, 109.4.

3,5-dichloroaniline (2g)



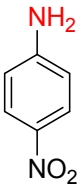
Yield 90% (144.9 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73-6.71 (m, 1H), 6.54-6.53 (m, 1H), 3.79 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 151.8, 134.6, 114.6, 112.2.

3-nitro aniline (2h)



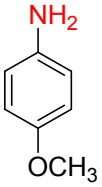
Yield 99% (136.6 mg); ^{1}H NMR (300 MHz, $CDCl_3$): 7.59-7.55 (m, 1H), 7.49-7.48 (m, 1H), 7.30-7.24 (m, 1H), 6.96-6.93 (m, 1H), 4.01 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 150.5, 149.2, 130.3, 120.4, 110.3, 107.5.

4-nitroaniline (2i)



Yield 97% (133.9 mg); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.96-7.93 (m, 2H), 6.72 (s, 2H), 6.62-6.58 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.2, 136.1, 126.9, 112.8.

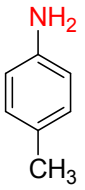
4-methoxyaniline (2j)



Yield 87% (109.5 mg) ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.65 (dd, J_1 = 9, J_2 = 2.1, 2H), 6.54 (dd, J_1 = 9, J_2 = 2.1 2H), 4.58 (s, 2H), 3.62 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 151.2, 142.7, 115.4, 114.9, 55.7.

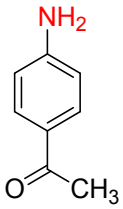
p-toluidine (2k)

Yield 89% (95.4 mg) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.00 (d, J_1 = 9, 2H), 6.65 (d, J_1 = 9, 2H), 3.47 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9,



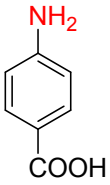
129.8, 127.8, 115.3, 20.5.

1-(4-aminophenyl) ethanone (2l)



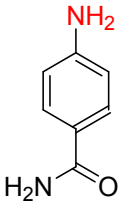
Yield 95% (128.4 mg); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.66 (dd, J_1 = 8.4, J_2 = 2.7, 2H), 6.56 (dd, J_1 = 8.4, J_2 = 2.4, 2H), 6.04 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 195.4, 154.1, 131.0, 125.3, 112.9, 26.3.

4-aminobenzoic acid (2m)



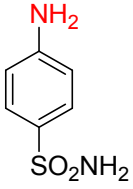
Yield 96% (131.6 mg); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.94 (s, 1H), 7.63 (d, J_1 = 8.1, 2H), 6.56 (d, J_1 = 8.1, 2H), 5.86 (s, 2H), ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.9, 153.6, 131.7, 117.4, 113.0.

4-aminobenzamide (2n)



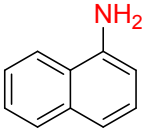
Yield 94% (127.9 mg); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.59 (d, J_1 = 6, 2H), 7.50 (s, 1H), 6.82 (s, 1H), 6.53 (d, J_1 = 9, 2H), 5.58 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.5, 152.1, 129.6, 121.5, 112.9.

4-aminobenzenesulfonamide (2o)



Yield 99% (170.5 mg); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.45 (d, J_1 = 6, 2H), 6.87 (s, 2H), 6.58 (d, J_1 = 9, 2H), 5.78 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ152.4, 130.5, 127.9, 112.9.

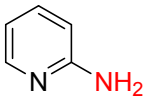
Naphthalene 1-amine (2p)



Yield 98% (140.3 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J*=3, 2H), 7.44-7.41 (m, 2H), 7.29-7.23 (m, 2H), 6.73 (d, *J=6,* 1H), 3.99 (s, 2H); ^{13}C NMR (75

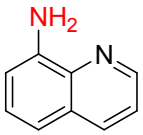
MHz, $CDCl_3$): δ142.1, 134.4, 128.6, 126.4, 125.9, 124.9, 123.7, 120.8, 119.0, 109.7.

2-amino pyridine (2q)



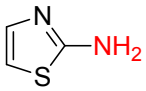
Yield 97% (91.28 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, *J* = 5.1 Hz, 1H), 7.41-7.36 (m, 1H), 6.62-6.58 (m, 2H), 6.48-6.45 (m, 1H), 4.46 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.2, 148.2, 137.4, 112.2, 108.4.

Quinolin-8-amine (2r)



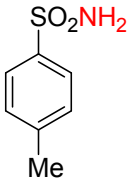
Yield 99% (142.7 mg); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.87-9.03 (m, 1H), 8.44-8.34 (m, 1H), 8.14 (m, 1H), 7.46-7.42 (m, 1H), 7.32-7.27 (m, 1H), 7.07-6.97 (m, 1H), 5.94 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 147.4, 145.7, 137.9, 136.3, 129.0, 128.0, 121.9, 114.2, 109.1.

Thiazol-2-amine (2s)



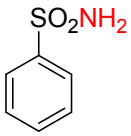
Yield 97% (97.13 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01-6.99 (m, 1H), 6.47-6.44 (m, 1H), 5.05 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 138.9, 108.7.

4-methylbenzenesulphonamide (2t)



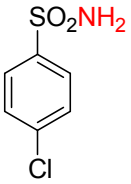
Yield 99% (169.5 mg); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.62 (d, *J* = 9 Hz, 2H), 7.28 (d, *J* = 9 Hz, 2H), 7.17 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 142.3, 141.9, 129.8, 126.1, 21.4.

Benzenesulphonamide (2u)



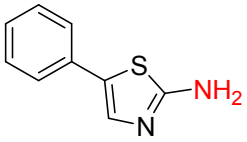
Yield 98% (154.04 mg); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.85-7.82 (m, 2H), 7.59-7.57 (m, 3H), 7.33 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 144.6, 132.2, 129.4, 126.0.

4-chlorobenzenesulphonamide (2v)



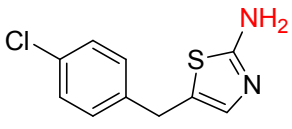
Yield 98% (187.8 mg); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.76-7.72 (m, 2H), 7.59-7.55 (m, 2H), 7.37 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 143.5, 137.0, 129.5, 128.1.

5-phenylthiazol-2-amine (2w)



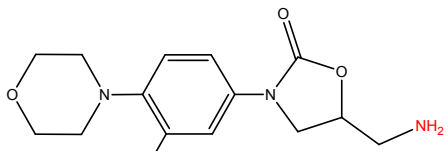
Yield 95% (167 mg); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.43-7.40 (m, 3H), 7.35-7.31 (m, 2H), 7.18 (s, 1H), 7.14 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.5, 135.7, 132.9, 129.4, 126.6, 125.4, 125.1.

5-(4-chlorobenzyl)thiazol-2-amine (2x)



Yield 96% (215 mg); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.28 (s, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 7.13 (s, 1H), 3.99 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.8, 138.1, 132.0, 130.8, 129.1, 124.4, 123.4, 31.5.

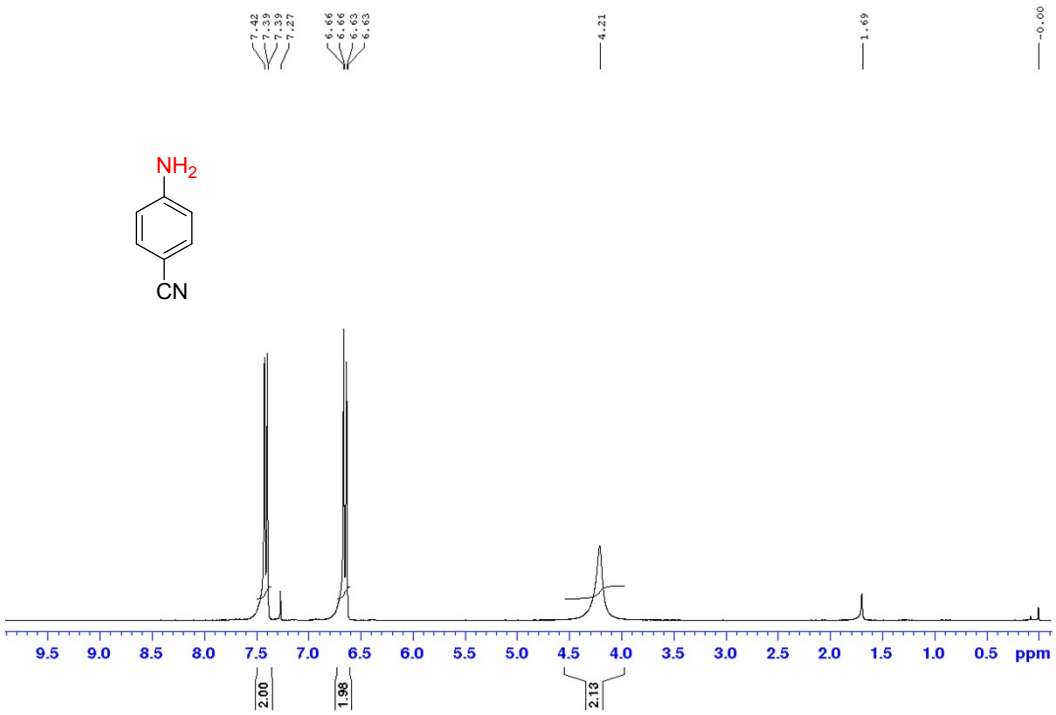
5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (2y)[5]



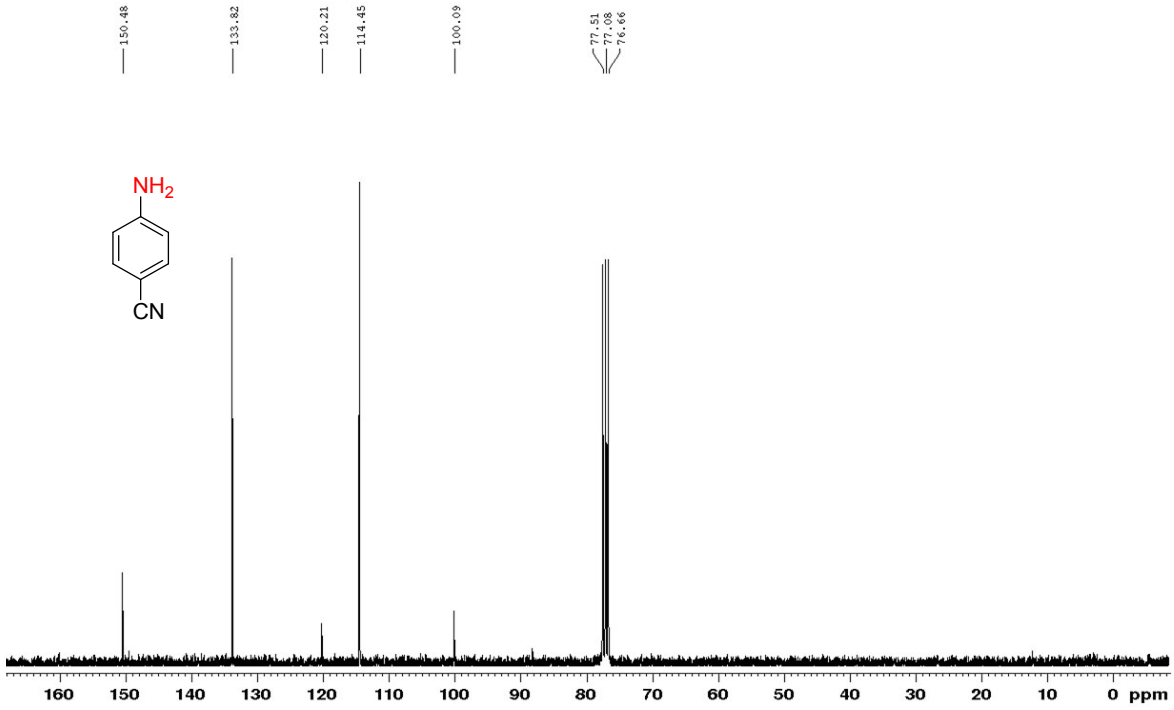
Yield 60% (177 mg); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.51 (d, J =15.3, 1H), 7.23-7.20 (m, 1H), 7.09-7.06 (m, 1H), 4.59 (s, 1H), 4.05-3.99 (m, 1H), 3.85-3.73 (m, 4H), 2.97 (s, 4H), 2.81 (s, 2H), 1.62 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.08

(d, $^{1}J_{CF}$ = 242.3 Hz), 154.8, 135.8 (d, $^{3}J_{CF}$ = 9 Hz), 134.2 (d, $^{3}J_{CF}$ = 10.5 Hz), 119.7 (d, $^{4}J_{CF}$ = 4.5 Hz), 114.4, 107.0 (d, $^{2}J_{CF}$ = 26.25 Hz), 74.5, 66.6, 51.2, 55.2, 47.5, 44.7.

Spectra of Compound 2a:

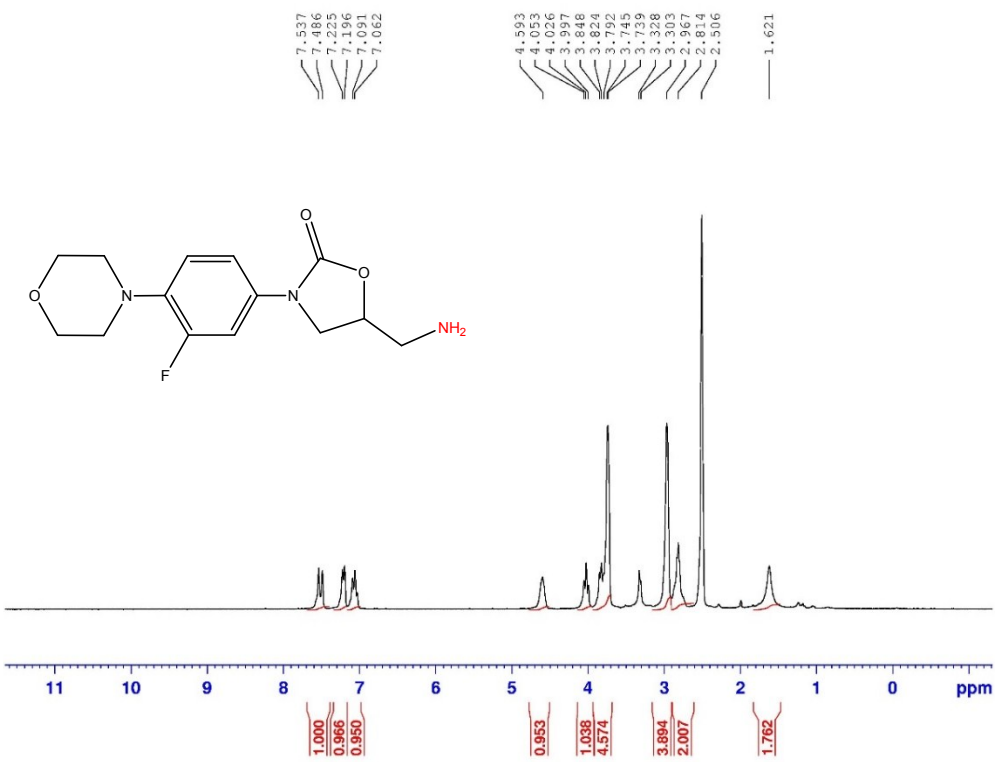


^{1}H NMR of Compound 2a

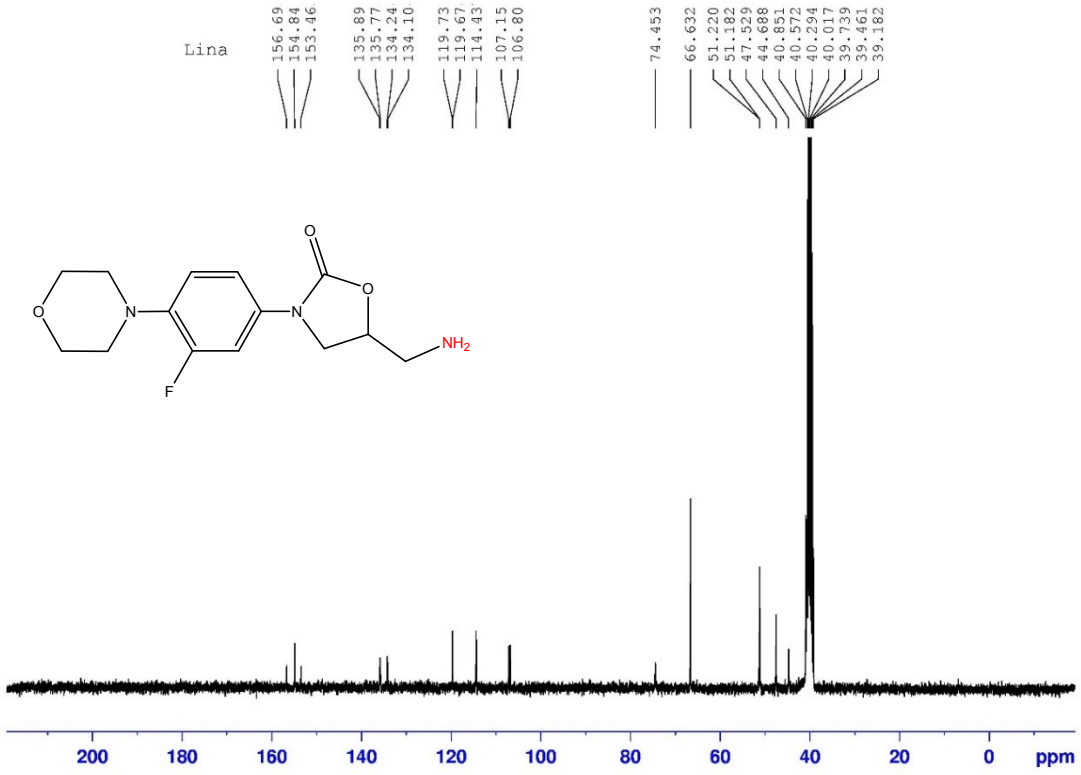


^{13}C NMR of Compound 2a

Spectra of Compound 2y:

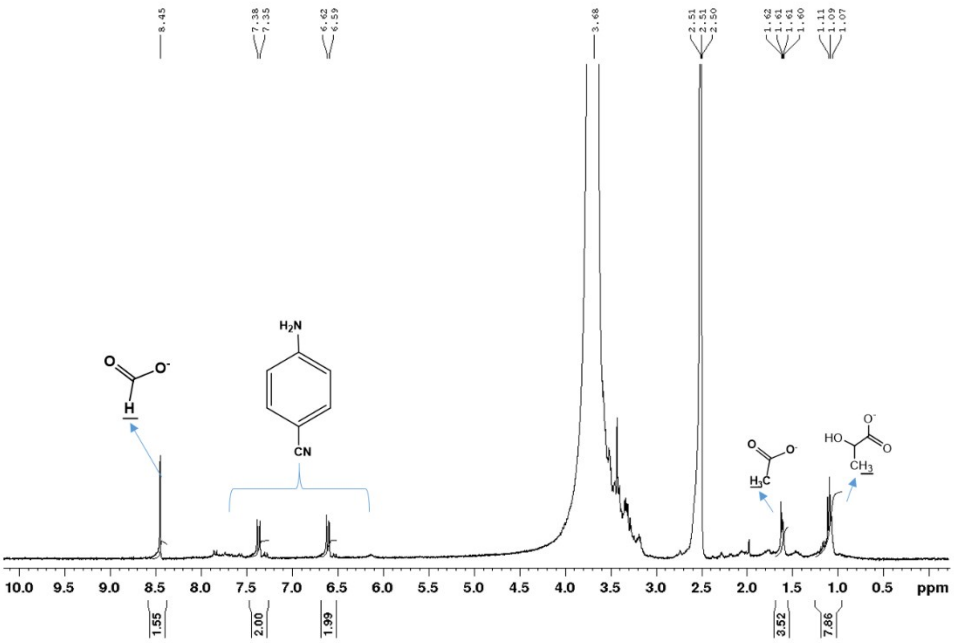


^{1}H NMR of Compound 2y

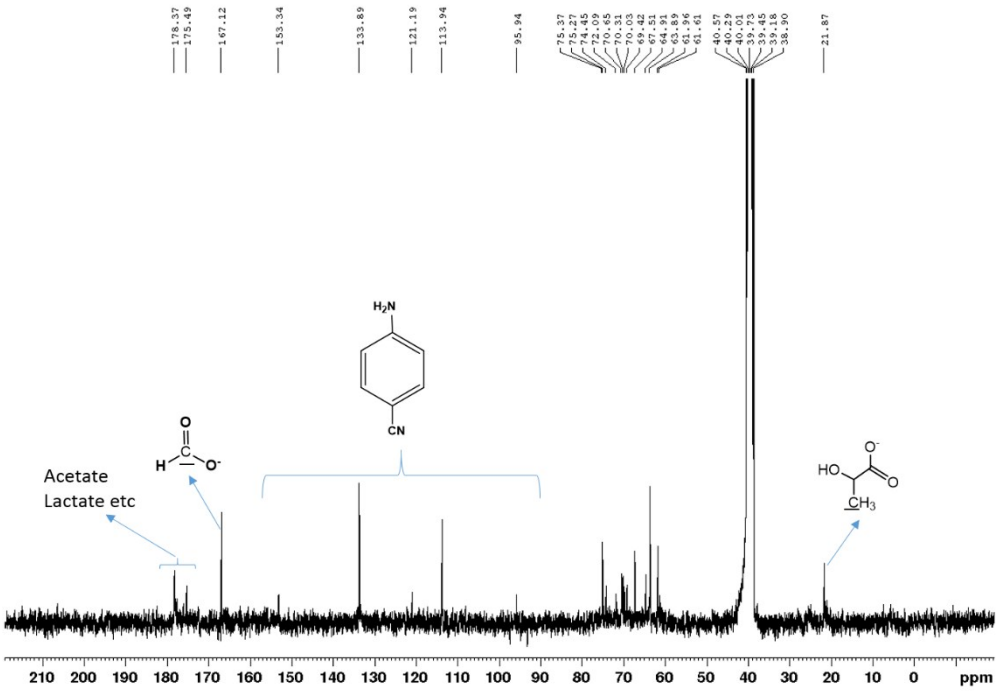


^{13}C NMR of Compound 2y

NMR spectra showing alkaline degradation of glucose in the reaction of 1a in D_2O



^{1}H NMR of Reaction Mixture of 1a in D_2O/DMSO-d_6



^{13}C NMR of Reaction Mixture of 1a in D_2O/DMSO-d_6

References:

1. U. Sharma, P. K. Verma, N. Kumar, V. Kumar, M. Bala and B. Singh, *Chem. Eur. J.*, 2011, **17**, 5903-4907.
2. S. Pagoti, S. Surana, A. Chauhan, B. Parasar, & J. Dash, *Catal. Sci. Tech.* 2013, **3**, 584-588.
3. N. Chandna, N. Chandak, P. Kumar, J. K. Kapoor, & P. K. Sharma, *Green Chem.* 2013, **15**, 2294-2301.
4. A. Khalil, J. A. Edwards, C. A. Rappleye and W. Tjarks, *Bioorg. Med. Chem.*, 2015, **23**, 532-547.
5. S. Fine, T. Nidam, & V. Braude US Pat. 7,291,614B2, 2007